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Title: Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

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Abstract

Objective: To investigate multimorbidity transitions from general practice populations across healthcare interfaces and the associated healthcare costs.

Design: Clinical-linkage database study.

Setting: Population (N=60,660) aged 40 years and over registered with 53 general practices in Stoke-on-Trent.

Participants: Population with six specified multimorbidity pairs were identified based on hypertension, diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and chronic kidney disease (CKD).

Main outcomes measures: Chronic disease registers were linked to accident and emergency (A&E) and hospital admissions for a 3-year time-period (2007-2009), and associated costs measured by Healthcare Resource Groups. Associations between multimorbid groups and direct healthcare costs were compared to their respective single disease groups using linear regression methods, adjusting for age, gender and deprivation.

Results: In the study population, there were 9735 patients with hypertension and diabetes (16%), 3574 with diabetes and CHD (6%), 2894 with diabetes and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Transition defined as at least one episode in each of the three year time-period, were as follows: patients with hypertension and DM had the fewest transitions in the 3-year time-period (37% A&E episode and 51% hospital admission), but CHF and CKD has the most transitions (67% A&E episode and 79% hospital admission).

The average 3-year total costs per multimorbid patient for A&E episodes ranged from £69 to £166 and for hospital admissions ranged from between £2289 to £5344. The adjusted costs were significantly higher for all six multimorbid groups compared to their respective single disease groups.

Conclusions: Specific common multimorbid pairs are associated with higher healthcare transitions and differential costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of integrated care.

Article summary

Article focus

- In the population there are large numbers of people who suffer with two or multiple chronic diseases at the same time.
- Most of the current evidence has focused on the impact of multimorbidity on health status and very few have investigated the transitions across healthcare and the associated costs.
- Whilst individual chronic diseases have been shown to be associated with high health care costs, whether specific multimorbid combinations have differential healthcare transitions and healthcare costs is unknown.

Key messages

- Specific multimorbid pairs are associated with different levels of healthcare transitions and costs relating to accident and emergency and to hospital admissions.
- Chronic disease pairs indicate the population level multimorbidity 'severity' as indicated by transitions and costs, with a range from diabetes and hypertension ('low severity'), diabetes and heart disease, diabetes and chronic kidney disease, COPD and heart disease, heart failure & COPD, to heart failure and chronic kidney disease ('high severity').
- Identification of multimorbidity type and linkage of information across healthcare interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

Strengths and limitations of this study

- The study was based on large scale data linking chronic disease registers from general practices to A&E episodes and hospital admissions
- The study highlights the innovative potential of linkage data between healthcare interfaces to inform healthcare delivery
- The study uses a specific, but a limited number of common chronic diseases to illustrate the approach to using linked data within a single large region of the UK

Background

Multimorbidity is an individual's experience of two or more illnesses at the same time. In ageing populations the numbers of people with such multimorbidity will increase substantially, and it is estimated that there are up to 20% of the British population (4 million people) who may experience such multimorbidity[1], with a projected further increase of 37% in the England & Wales population aged 50 years and over by the year 2031. This means that the current focus of health care delivery on specific disease-focus outcomes will have to be complemented by a Public Health priority focusing on multimorbidity in older populations.

Current evidence on multiple disease in the same person has shown that this is a common problem, which has high impact on an individual's health and on the use of health care resources.[2,3,4] However, people may also experience transitions across different healthcare interfaces, especially as delivery of chronic disease is orientated around individual healthcare pathways. Once a person experiences a number of different diseases, the issue then becomes how the person interacts with different healthcare interfaces. Current research has shown that in specific settings, such as general practice[5] or hospitals, multimorbidity is common in the encounters that are present in the disease-care pathways.[6,7] However, there is little empirical data on how multimorbidity influences transitions across different healthcare interfaces and whether specific multimorbidity combinations are more likely to be associated with higher healthcare presentations, such as Accident and Emergency (A&E) episodes or hospital admissions. Routine coding of such patients encounters now occurs in clinical practice, A&E and hospitals, and technological developments allow the linkage of clinical information across these interfaces.[8] These developments allow for the potential for targeted prevention and new models of healthcare interventions for patients who experience multiple chronic diseases at the same time.

The other key area of focus is how cost-effective care pathways can be developed. By understanding how multimorbidity influences interface presentation and the associated healthcare costs, it can be explored as to whether healthcare cost can be 'benchmarked' for specific conditions and combinations of conditions.[9] Currently much of the chronic disease healthcare delivery pathways has aligned along single-disease lines, for example diabetes, chronic obstructive airways disease or heart failure. So the potential range of multimorbidity model of care could range from joint clinics (e.g. diabetes and renal) to the holistic clinical assessment conducted by elderly care physicians.[10,11]

However, one could argue the next simple step from single disease pathway care to a multimorbidity approach, is understanding pair combinations which link to at least two individual disease care pathways, and which we use in this study by selecting common chronic diseases in the older population. Using a large linkage dataset we investigated the clinical hypothesis as to whether specific chronic disease multimorbidity pairs are associated with distinct health care transitions and associated costs.

Methods

Design

The design of the study was a cross-sectional clinical linkage study of the population aged 40 years and over on chronic disease registers to transition data on A&E episode or hospital admission in a 3-year time-period (1st January 2007 to 31st December 2009).

Setting

The setting is an urban population of around 240,000 which focuses around the city of Stoke-on-Trent, which is one of the most deprived in England & Wales and has some of the highest levels of chronic disease prevalence and over half of areas are in the most deprived 20% in England.[12]

Clinical linkage datasets

Chronic disease registers

The local Primary Care Trust oversees 53 general practices and all practices have been participating in a national and local quality improvement framework[13] for specific chronic diseases, and in recording clinical data through regular data audits and checks. For specified conditions, using the Read Code classification[14], General Practitioners (GPs) and their teams had recorded clinical data on disease registers for their population. These practices contributed to the construction of a clinical database, which for this study covers a 3-year time-period. From this database, all adults on chronic disease registers for the following six conditions were identified: hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and chronic kidney disease (CKD).

Multimorbidity definitions

Whilst multimorbidity could be characterised for the study as any number or multiple combinations, we selected 'pairs' as the basic measure of investigating multimorbidity. The 'pairs' provides the basis for clinically intuitive understanding of how two chronic disease pathways might combine together, but with six study chronic diseases chosen, the potential number of pairs could be 6x6=36. Therefore, six example pairs were chosen to represent the range of chronic diseases onsets from mid-life to old-age and included: (i) DM and HT; (ii) DM and CHD; (iii) DM and CKD; (iv) COPD and CHD; (v) COPD and CHF; and (vi) CHF and CKD. These multimorbid pairs were then compared to their respective 'index' conditions, for example, HT and DM multimorbidity was compared to the group with HT without DM (expressed as HT+ DM-) and DM without HT (DM+ HT-). Each multimorbid group and their respective 'index' conditions represent a within group (see **Table 1** for annotation of all study defined groups) and separate clinical hypothesis of the association between multimorbidity and healthcare outcomes. In addition to age and gender data available from the general practice records, and the Index of Multiple Deprivation (IMD) was used as a measure of socio-economic status. The IMD is a measure of multiple deprivation at the small area level.[15] Based on Census data the score combines a number of indicators, including economic, social and housing issues, into a single deprivation score for each small area in England.

Healthcare transitions data: A&E episodes and hospital admissions

Using the unique NHS Number allocated to an individual patient, a dataset was created linking their clinical data from general practice to any other information such as A&E attendance and hospital admissions (planned and unplanned) for the time period 1st January 2007 to 31st December 2009. The total number of attendances in the study time period for each A&E type including minor injury units and walk-in centres were included. Whilst there are a number of hospital providers within the region, the single major provider of emergency and acute hospital services for the city is the University Hospital of North Staffordshire (UHNS) NHS Trust. Hospital admissions were based on Hospital Episode Statistics (HES), which contain records for all NHS patients admitted to English hospitals in each financial year. These A&E and hospital data are means by which Primary Care (PCT) Commissioners arrange payment from the purchaser to the acute hospital Trust provider.[16] Linking these clinical databases make it possible to track healthcare patterns of individual patients. We used these data therefore to establish the

natural history of patients with multimorbidity and transitions across the A&E and hospital interfaces.

Healthcare transitions cost

For each transition activity, the allocated Healthcare Resource Group (HRG) was used as a measure of cost for an A&E episode or a hospital admission in the 3-year time-period. A HRG is a group of clinically similar treatments and care that require similar levels of healthcare resource. It allows commissioners to understand their activity in terms of the types of patients they care for and the treatments they undertake.[17,18] HRGs are currently used as a means of determining cost for individual patients in each financial year, depending on their healthcare use. From the individual-level HRG cost data for A&E episode or hospital admission, data was aggregated to the population-level costs for the specified multimorbidity groups for the whole of the 3-year time-period. Individual-level data were anonymised by the Public Health Intelligence Team and subsequently linked for analyses using study identifier by the project team, and provision of the anonymous data was made under existing service agreements.

Analyses

The multimorbidity populations are described by age bands (40-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, 90 years and over), gender and deprivation. The IMD score for the study population was summarised into quartiles ranging from quartile 1 (least deprived) to quartile 4 (most deprived).

Interface transitions for the six multimorbid groups and their respective index conditions were defined as follows. A&E transitions were first summarised as at least one episode in any one of the 3 years, and so does not include multiple episodes within the same year. A similar approach was used for summarising the hospital admissions. Chi square tests were used to assess trends in the association between study defined groups and recurrent A&E episodes and hospital admissions (defined as at least one in each of the 3 years). These data are then presented as counts measured from 0 (no episodes or admissions), 1 (one episode in any one of the 3 years), 2 (two episodes in any two of the 3 years), and 3 (at least one episode in all 3 years). ANOVA and ANCOVA with actual age, gender and IMD as covariates were used to estimate the significance of mean differences of number of A&E episodes, hospital admissions and costs, within each of

the multimorbid groups, comparing the pairs of diseases to their respective index diseases.

Total costs for the study time period were estimated for each individual patient who had any A&E episode or hospital admissions, and here the total costs relate to all A&E episodes and hospital admissions over the 3 year time-period. Using linear regression methods, the difference in total cost per patient over the 3 years for each multimorbid group was compared to the respective index conditions was assessed, adjusting for age, gender and deprivation. Within each of the six multimorbid groups, the regression coefficient was tested for significance differences from their respective reference category with cost allocation as zero (0).

Results

From a study population of 60,660 patients aged 40 years and over on specific chronic disease registers in a 3-year time-period, there were 9735 patients with HT and DM (16%), 3574 with DM and CHD (6%), 2894 with DM and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Socio-demographic characteristics of multimorbid pairs

Multimorbid pairs, which included DM and HT or CHD, showed age-related differences (**Table 2**). Within the DM and CKD multimorbid group, there was a higher proportion of older patients aged 70 years and over (51%), than within the DM and CHD group or the HT and DM multimorbid group. There were more women (64%) than men within the DM and CKD group, than the other two DM multimorbid groups, but the deprivation distributions were similar. Within the COPD and CHF multimorbid groups, there was a higher proportion of older patients aged 70 years and over (75%), compared to COPD and CHD, but within the COPD and CHD group there were more men (62%) than women. The CHF and CKD multimorbid group had the highest proportion who were aged 80 years and over (50%), and this group had more women than men.

Multimorbidity transitions across accident & emergency interface

Patients with HT and DM had the highest proportion without an A&E episode in the 3-year time-period (63%), but the patients with CKD and CHF had the lowest proportion without an A&E episode in the 3-year time-period (33%) (**Table 3**). The same figures for

other multimorbid groups were as follows: DM & CHD 52%; DM & CKD 51%; COPD & CHD 44%; and CHF & COPD 42%.

The proportion of patients with recurrent A&E episodes (defined as at least one episode in each of the 3 years) for multimorbid groups was as follows: HT and DM 2%, DM & CHD 4%, DM & CKD 3%, COPD & CHD 5%, CHF & COPD 7% and CKD & CHF 6%. These associations and increase across the groups was even more evident for patients who had had an A&E episode in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and recurrent A&E episodes (p<0.001).

Multimorbidity transitions across hospital admission interface

Patients with HT and DM had the highest proportion without a hospital admission in the 3-year time-period (49%), but the patients with CKD and CHF had the lowest proportion without a hospital admission in the 3-year time-period (21%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 39%; DM & CKD 37%; COPD & CHD 31%; and CHF & COPD 28%.

The proportion of patients with recurrent hospital admissions (defined as at least one in each of the 3 years) for multimorbid groups was as follows: HT and DM 6%; DM & CHD 10%; DM & CKD 10%; COPD & CHD 12%; CHF & COPD 13%; and CKD & CHF 13%. These associations and increase across the groups was even more evident for patients who had had a hospital admission in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index conditions, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission (p<0.001).

Health care costs at the accident & emergency transition

Patients with HT and DM had the lowest mean A&E costs in the 3-year time-period (total £69), but the highest figure was for patients with CHF and COPD or CKD (around £166) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £104; DM & CKD £105; COPD & CHD £138; and CHF & COPD £164.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher A&E costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two

notable groups. The A&E costs were £13 lower for the index CHD group compared to index COPD group, and £31 lower for index CKD group than the CHF group (**Table 3**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher A&E costs (p<0.001).

Healthcare costs at the hospital admission transition

Patients with HT and DM had the lowest mean hospital admissions costs in the 3-year time-period (total £2289), but patients with CHF and CKD had the highest costs (£5344) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £3372; DM & CKD £3642; COPD & CHD £3992; and CHF & COPD £4901.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher hospital admission costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The hospital admission costs were £152 lower for the index CHD group compared to index COPD group, and £629 lower for index CKD group than the CHF group (**Table 4**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission costs (p<0.001).

The six multimorbid groups were selected on the basis of age-related onsets. However, comparing the findings for the six multimorbid pairs, after age adjustment, also showed that these groups can be placed into an order of an increasing association between the 'severity' of multimorbid pair and the likelihood of A&E episodes and associated costs, or hospital admissions and associated costs over the 3-year time-period. The 'severity' of health care impact can be ordered as follows: DM and HT ('low severity'), DM and CHD, DM and CKD, COPD and CHD, CHF & COPD, and CHF and CKD ('high severity') (**Tables 3 and 4**).

Discussion

Our large scale study in a chronic disease population showed that patients with specific multimorbidity pairs had distinct variations in healthcare transitions and in the associated healthcare costs. Whilst age is a specific indicator for the type of multiple chronic disease, adjustment for socio-demographic factors, still showed that specific

multimorbidity pairs were associated with higher number of healthcare transitions compared to their respective index groups. Furthermore, these multimorbidity associations suggest that they can be ordered into a 'severity of healthcare impact', after adjusting for age. In this spectrum, multimorbidity such as hypertension and diabetes represents one end of the healthcare cost spectrum and chronic heart failure and chronic kidney disease representing the higher and most costly end of healthcare impact.

The implications of this multimorbidity study covering a 3-year time-period relates to the number of transitions and costs of transitions. The study shows that patients with specific multimorbidity has higher number of annual A&E episodes or hospital admissions and costs, which means that this provides a potential mechanism for targeting patients for intervention across the healthcare interfaces. Since this information could potentially be linked across the interface, it also provides the basis for intervention once initial transitions have occurred to prevent future unnecessary transitions from general practice to A&E or hospital admission.

The study was based on large scale data available from 53 general practices in one of the most deprived regions in England and over a long term time period of 3 years. The current national quality improvements approaches have been based on establishing chronic disease registers in clinical practice and aim at improving care for the individual patient.[12,19] However such registers also provide the basis for defining population-level impacts and for providing the integration between public health prevention (general practice or local area) and individual-level care. The definition of multimorbidity, focusing on 'pairs' also means that it allows easier interpretation of the current individual pathways of care and begins to provide insight into how these might be integrated. For example, hypertension, diabetes and coronary heart disease are often jointly managed in general practice, but in healthcare transitions, specialist care could be delivered by nephrology (hypertension), diabetes or cardiology. However in severe chronic disease states, such as COPD, CHF and CKD, which are often jointly managed between general practice and hospital-based care, such 'multimorbidity pair' approach allows for the integration of care for high cost patients who may be cared for by several healthcare teams in different individual care pathways.

Whilst this was a large scale study, the cross-sectional findings relate to one region of England. The patterns of transitions may differ in other regions, especially as services moved to different integrated models, but the relative associations for multimorbid

groups compared to the index groups provide the best available estimates on the impact on transitions and costs. These cost estimations and relative are conservative as the reference comparison groups had one of the two multimorbid conditions, whereas a non-index reference group without either pair condition would have magnified the relative cost differences. Whilst new integrated models of care are developing[20], such care will still need to differentiate between the acute health needs of the patient with a chronic disease addressed by specialist intervention, and the chronic health needs and monitoring that will be addressed by general practice and community teams. The study definitions also focused on pairs of conditions but all groups were not exclusive, and there was some overlap. For example diabetes was paired with hypertension, coronary heart disease and chronic kidney disease, which indicates an overlap, but these results showed that different pairs with the same index condition (e.g. diabetes) have distinct associations with healthcare transitions and costs.

The chronic disease registers from general practice were part of local and national initiatives, and such data are now used widely in performance and payment reporting, and healthcare studies.[19] The healthcare transition data also are part of national performance and payment reporting, and have also been used in healthcare studies. The recording of these transition episodes (A&E or hospital admission) will be accurate as the healthcare costs are based on the HRG allocated to each individual patient, and which is part of the cost transaction process between healthcare commissioner (PCT) and the provider (hospital). Furthermore the transitions data and cost data are part of national validation processes.[16,21] In this study, the primary objective was to test the clinical hypothesis that different multimorbidity pairs showed variations in overall healthcare transitions, and therefore does not include the attempt to characterise the precise nature of each transition episode. The estimated costs for these patient populations are also an under-estimate since they do not include ongoing healthcare costs in general practice and community care.

Previously there have been few studies on multimorbidity and costs in specific settings[22,23], but there is a lack of healthcare transitions data, and the hypothesis that a study of specific 'disease pairs' may provide insight into healthcare presentation and costs has not been previously tested. Much of the current multimorbidity research has focused on the 'burden' as exemplified by the number of conditions that patient's experience, but the key limitation with the 'counting' approach is the lack of differentiation of how it links into the current individual disease-designed pathways.

Arguably, it is better conceptualise this issue into 'which pairs' and link it practically to the individual disease pathways which have been devised in terms of chronic disease model of care.[24] Notably the notion of chronic disease and depression has been well constructed in the psychiatric field.[25] This 'disease pair' approach provides a simple and clinically intuitively approach that can be readily used in actual clinical practice, and a means by which local policy decisions can incorporate estimated costs for healthcare transitions.

This cross-sectional study provides the basis for the innovative linking of data, and understanding the healthcare 'journey' for the patient with different chronic diseases. Further studies would address issues such as multiple healthcare transitions, combining different interfaces (for example, identifying patients who attend A&E regularly and are admitted regularly) and the underlying and precise clinical reasons for the healthcare costs. For example, healthcare transitions may cover community care, and wider transitions could include social care. The associations shown in this study also need to be complemented by the temporal investigation between chronic disease pairs and subsequent impact on the time between health care transitions.

In conclusion, our study showed that specific multimorbid pairs compared to their index morbidity, indicated the level of transitions across healthcare interfaces and the associated total healthcare costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

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Conflicts of interests: None.

Contributors: JU coordinated the study data collection and contributed to the writing of the manuscript. PWK was involved in study design and developed the statistical approaches. ZI was involved in the study design, interpretation and writing of the paper. UTK conceived and designed the study, was involved with analysis, interpretation and contributed to the writing of this manuscript. All authors have contributed and approved the final version of this manuscript.

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Table 1: Study groups

Annotation	Study groups
HT+ DM-	Hypertension *without* diabetes mellitus
DM+ HT-	Diabetes mellitus *without* hypertension
HT & DM	Multimorbidity of hypertension *and* diabetes mellitus
DM+ CHD-	Diabetes mellitus *without* coronary heart disease
CHD+ DM-	Coronary heart disease *without* diabetes mellitus
DM & CHD	Multimorbidity of diabetes mellitus *and* coronary heart disease
DM+ CKD-	Diabetes mellitus *without* chronic kidney disease
CKD+ DM-	Chronic kidney disease *without* diabetes mellitus
DM & CKD	Multimorbidity of diabetes mellitus *and* chronic kidney disease
COPD+ CHD-	Chronic obstructive pulmonary disease *without* coronary heart disease
CHD+ COPD-	Coronary heart disease *without* chronic obstructive pulmonary disease
COPD & CHD	Multimorbidity of chronic obstructive pulmonary disease *and* coronary heart disease
COPD+ CHF-	Chronic obstructive pulmonary disease *without* chronic heart failure
CHF+ COPD-	Chronic heart failure *without* chronic obstructive pulmonary disease
CHF & COPD	Multimorbidity of chronic heart failure *and* chronic obstructive pulmonary disease
CHF+ CKD-	Chronic heart failure *without* chronic kidney disease
CKD+ CHF-	Chronic kidney disease *without* chronic heart failure
CKD & CHF	Multimorbidity of chronic kidney disease *and* chronic heart failure

Table 2: Socio-demographic characteristics of the multimorbid study pairs

Groups	HT & DM *No (%)* (n=9735)	DM & CHD *No (%)* (n=3574)	DM & CKD *No (%)* (n=2894)	CHD & COPD *No (%)* (n=1855)	CHF & COPD *No (%)* (n=754)	CHF & CKD *No (%)* (n=1425)
40-49 years	866 (8.9)	152 (4.2)	48 (1.7)	22 (1.2)	4 (0.5)	6 (0.4)
50-59 years	2043 (21.0)	533 (14.9)	227 (7.8)	179 (9.6)	42 (5.5)	49 (3.4)
60-69 years	2866 (29.4)	1067 (29.8)	645 (22.3)	499 (26.8)	140 (18.6)	177 (12.4)
70-79 years	2686 (27.6)	1219 (34.1)	1200 (41.3)	710 (38.3)	298 (39.3)	488 (34.2)
80-89 years	1152 (11.9)	552 (15.5)	691 (24.0)	409 (22.1)	236 (31.6)	594 (41.9)
90 years and over	122 (1.3)	51 (1.5)	83 (2.9)	36 (2.0)	34 (4.5)	111 (7.7)
Men	5016 (51.5)	2162 (60.4)	1055 (36.4)	1152 (62.1)	427 (56.4)	549 (38.5)
Women	4719 (48.5)	1412 (39.6)	1839 (63.6)	703 (37.9)	327 (43.6)	876 (61.5)
Quartile 1* Least deprived	2044 (21.1)	691 (19.5)	596 (20.7)	249 (13.5)	109 (14.5)	300 (21.1)
Quartile 2	2335 (24.1)	785 (22.1)	652 (22.6)	428 (23.2)	171 (22.8)	340 (23.9)
Quartile 3	2541 (26.2)	934 (26.3)	801 (28.9)	527 (28.5)	205 (27.3)	401 (28.2)
Quartile 4 Most deprived	2768 (28.6)	1142 (32.2)	831 (28.9)	644 (34.8)	265 (35.3)	379 (26.7)

**Deprivation measured using the Index of Multiple Deprivation; HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 3: Multimorbidity transitions across A&E and hospital admission interface over 3-years

Study Groups†	A & E episodes				Hospital admissions			
	0	1	2	3	0	1	2	3
	No (%)	*No (%)*	*No (%)*	No (%)	*No (%)*	*No (%)*	*No (%)*	*No (%)*
HT+ DM-	26019 (68.6)	8903 (23.5)	2466 (6.5)	548 (1.4)	21957 (54.0)	10443 (27.5)	4223 (11.1)	1313 (3.5)
DM+ HT-	2733 (63.2)	1154 (26.4)	372 (8.4)	96 (2.1)	2343 (54.0)	1192 (27.5)	601 (13.8)	204 (4.7)
HT & DM	6168 (63.4)	2581 (26.5)	776 (8.0)	210 (2.2)	4800 (49.3)	2888 (29.7)	1456 (15.0)	591 (6.1)
DM+ CHD-	7048 (67.1)	2580 (24.6)	703 (6.7)	170 (1.6)	5766 (54.9)	2993 (28.2)	1403 (12.7)	490 (4.2)
CHD+ DM-	6223 (57.6)	3175 (29.4)	1133 (10.5)	276 (2.6)	4842 (44.8)	3482 (32.2)	1813 (16.8)	670 (6.2)
DM & CHD	1863 (52.1)	1145 (32.0)	436 (12.2)	130 (3.6)	1377 (38.5)	1123 (31.4)	721 (20.2)	353 (9.9)
DM+ CKD-	7440 (66.5)	2761 (24.7)	775 (6.9)	205 (1.8)	6083 (54.4)	3142 (28.1)	1438 (12.9)	518 (4.6)
CKD+ DM-	5137 (57.3)	2733 (30.5)	893 (10.0)	195 (2.2)	3923 (43.8)	3056 (34.1)	1502 (16.8)	477 (5.3)
DM & CKD	1471 (50.8)	964 (33.3)	364 (12.6)	95 (3.3)	1060 (36.6)	938 (32.4)	619 (21.4)	277 (9.6)
COPD+ CHD-	3013 (56.8)	1568 (29.6)	546 (10.3)	177 (3.3)	2443 (46.1)	1665 (31.4)	843 (15.9)	353 (6.7)
CHD+ COPD-	7267 (58.0)	3689 (29.5)	1261 (10.1)	309 (2.5)	5641 (45.0)	3973 (31.7)	2108 (16.8)	804 (6.4)
COPD & CHD	819 (44.2)	631 (34.0)	308 (16.6)	97 (5.2)	578 (31.2)	632 (34.1)	426 (23.0)	219 (11.8)

COPD+ CHF-	3519 (54.9)	1940 (30.3)	723 (11.3)	223 (3.5)	2810 (43.9)	2018 (31.5)	1102 (17.2)	475 (7.4)
CHF+ COPD-	1346 (46.7)	990 (34.3)	440 (15.3)	108 (3.7)	978 (33.9)	996 (34.5)	645 (22.4)	265 (9.2)
CHF & COPD	313 (41.5)	259 (34.4)	131 (17.4)	51 (6.8)	211 (28.0)	279 (37.0)	167 (22.1)	97 (12.9)
CHF+ CKD-	1173 (53.0)	665 (30.0)	295 (13.3)	80 (3.6)	884 (39.9)	737 (33.3)	414 (18.7)	178 (8.0)
CKD+ CHF-	6122 (58.7)	3113 (29.9)	981 (9.4)	211 (2.0)	4678 (44.9)	3456 (33.1)	1723 (16.5)	570 (5.5)
CKD & CHF	481 (33.4)	595 (41.3)	284 (19.7)	80 (5.6)	305 (21.4)	538 (37.8)	398 (27.9)	184 (12.9)

† *minus sign indicates absence of disease and positive sign indicates presence, HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 4: Multimorbidity transitions across A&E episodes and hospital admissions and associated costs over 3-years

Study Groups	3-year AE £ costs Mean (SD)	Adjusted £ Regression Estimates (SE)	*p*-value	3-year IP £ costs Mean (SD)	Adjusted £ Regression Estimates (SE)	*p*-value
HT+ DM-	55 (132)	0		1647 (4085)	0	
DM+ HT-	69 (162)	20 (2)	<.001	2061 (4490)	595 (68)	<.001
HT & DM	69 (152)	14 (2)	<.001	2289 (4585)	607 (48)	<.001
DM+ CHD-	57 (124)	0		1825 (3977)	0	
CHD+ DM-	84 (175)	22 (2)	<.001	2512 (5825)	431 (73)	<.001
DM & CHD	104 (219)	42 (3)	<.001	3372 (5789)	1270 (101)	<.001
DM+ CKD-	60 (143)	0		1850 (3996)	0	
CKD+ DM-	80 (144)	4 (2)	0.14	2559 (4380)	403 (73)	<.001
DM & CKD	105 (190)	30 (3)	<.001	3642 (6063)	1480 (97)	<.001
COPD+ CHD-	96 (214)	0		2642 (4814)	0	
CHD+ COPD-	81 (180)	-13 (4)	<.001	2537 (5812)	-152 (92)	.097
COPD & CHD	138 (219)	40 (5)	<.001	3992 (5775)	1158 (151)	<.001
COPD+ CHF-	100 (211)	0		2769 (4925)	0	
CHF+ COPD-	120 (192)	17 (5)	<.001	3877 (5732)	904 (125)	<.001
CHF & COPD	166 (242)	64 (8)	<.001	4901 (6199)	1954 (206)	<.001
CHF+ CKD-	108 (176)	0		3282 (4880)	0	
CKD+ CHF-	75 (139)	-31 (4)	<.001	2477 (4404)	-629 (114)	<.001
CKD & CHF	164 (238)	52 (5)	<.001	5344 (6907)	2116 (163)	<.001

DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease HT=hypertension,

Title: Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

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Abstract

Objective: To investigate multimorbidity transitions from general practice populations across two healthcare interfaces and the associated direct healthcare-related costs.

Design: Clinical-linkage database study.

Setting: Population (N=60,660) aged 40 years and over registered with 53 general practices in Stoke-on-Trent, Staffordshire.

Participants: From the population aged 40 years and over six specified multimorbidity pairs were identified based on hypertension, diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and chronic kidney disease (CKD).

Main outcomes measures: Chronic disease registers were linked to accident and emergency (A&E) and hospital admissions episodes for a 3-year time-period (2007-2009), and associated costs measured by Healthcare Resource Groups. Associations between multimorbid groups and direct healthcare costs were compared to their respective single disease groups using linear regression methods, adjusting for age, gender and deprivation.

Results: In the study population, there were 9735 patients with hypertension and diabetes (16%), 3574 with diabetes and CHD (6%), 2894 with diabetes and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Transition defined as at least one episode in each of the three year time-period, were as follows: patients with hypertension and DM had the fewest transitions in the 3-year time-period (37% had had an A&E episode and 51% a hospital admission), but CHF and CKD has the most transitions (67% had had an A&E episode and 79% a hospital admission). The average 3-year total costs per multimorbid patient for A&E episodes ranged from £69 to £166 and for hospital admissions ranged from between £2289 to £5344. The adjusted costs were significantly higher for all six multimorbid groups compared to their respective single disease groups.

Conclusions: Specific common multimorbid pairs are associated with higher healthcare transitions and differential costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of integrated care.

Article summary

Article focus

- In the population there are large numbers of people who suffer with two or multiple chronic diseases at the same time.
- Most of the current evidence has focused on the impact of multimorbidity on health status and very few have investigated the transitions across healthcare and the associated costs.
- Whilst individual chronic diseases have been shown to be associated with high health care costs, whether specific multimorbid combinations have differential healthcare transitions and healthcare costs is unknown.

Key messages

- Specific multimorbid pairs are associated with different levels of healthcare transitions and costs relating to accident and emergency and to hospital admissions.
- Chronic disease pairs indicate the population level multimorbidity 'severity' as indicated by transitions and costs, with a range from diabetes and hypertension ('low severity'), diabetes and heart disease, diabetes and chronic kidney disease, COPD and heart disease, heart failure & COPD, to heart failure and chronic kidney disease ('high severity').
- Identification of multimorbidity type and linkage of information across healthcare interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

Strengths and limitations of this study

- The study was based on large scale data linking chronic disease registers from general practices to A&E episodes and hospital admissions
- The study highlights the innovative potential of linkage data between healthcare interfaces to inform healthcare delivery
- The study uses a specific, but a limited number of common chronic diseases to illustrate the approach to using linked data within a single large region of the UK

Background

Multimorbidity is an individual's experience of two or more illnesses at the same time. In ageing populations the numbers of people with such multimorbidity will increase substantially, and it is estimated that there are up to 20% of the British population (4 million people) who may experience such multimorbidity[1], with a projected further increase of 37% in the England & Wales population aged 50 years and over by the year 2031. This means that the current focus of health care delivery on specific disease-focus outcomes will have to be complemented by a Public Health priority focusing on multimorbidity in older populations.

Current evidence on multiple disease in the same person has shown that this is a common problem, which has high impact on an individual's health and on the use of health care resources.[2,3,4] However, people may also experience transitions across different healthcare interfaces, especially as delivery of chronic disease is orientated around individual healthcare pathways. Once a person experiences a number of different diseases, the issue then becomes how the person interacts with different healthcare interfaces. Current research has shown that in specific settings, such as general practice[5] or hospitals, multimorbidity is common in the encounters that are present in the disease-care pathways.[6,7] However, there is little empirical data on how multimorbidity influences transitions across different healthcare interfaces and whether specific multimorbidity combinations are more likely to be associated with higher healthcare presentations, such as Accident and Emergency (A&E) episodes or hospital admissions. Routine coding of such patients encounters now occurs in clinical practice, A&E and hospitals, and technological developments allow the linkage of clinical information across these interfaces.[8] These developments allow for the potential for targeted prevention and new models of healthcare interventions for patients who experience multiple chronic diseases at the same time.

The other key area of focus is how cost-effective care pathways can be developed. By understanding how multimorbidity influences interface presentation and the associated healthcare costs, it can be explored as to whether healthcare cost can be 'benchmarked' for specific conditions and combinations of conditions.[9] Currently much of the chronic disease healthcare delivery pathways has aligned along single-disease lines, for example diabetes, chronic obstructive airways disease or heart failure. So the potential range of multimorbidity model of care could range from joint clinics (e.g. diabetes and renal) to the holistic clinical assessment conducted by elderly care physicians.[10,11]

However, one could argue the next simple step from single disease pathway care to a multimorbidity approach, is understanding pair combinations which link to at least two individual disease care pathways, and which we use in this study by selecting common chronic diseases in the older population. Using a large linkage dataset we investigated the clinical hypothesis as to whether specific chronic disease multimorbidity pairs are associated with distinct health care transitions and associated costs.

Methods

Design

The design of the study was a cross-sectional clinical linkage study of the population aged 40 years and over on chronic disease registers to transition data on A&E episode or hospital admission in a 3-year time-period (1st January 2007 to 31st December 2009).

Setting

The setting is an urban population of around 240,000 which focuses around the city of Stoke-on-Trent, which is one of the most deprived in England & Wales and has some of the highest levels of chronic disease prevalence and over half of areas are in the most deprived 20% in England.[12]

Clinical linkage datasets

Chronic disease registers

The local Primary Care Trust oversees 53 general practices and all practices have been participating in a national and local quality improvement framework[13] for specific chronic diseases, and in recording clinical data through regular data audits and checks. For specified conditions, using the Read Code classification[14], General Practitioners (GPs) and their teams had recorded clinical data on disease registers for their population. These practices contributed to the construction of a clinical database, which for this study covers a 3-year time-period. From this database, all adults on chronic disease registers for the following six conditions were identified: hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and chronic kidney disease (CKD).

Multimorbidity definitions

Whilst multimorbidity could be characterised for the study as any number or multiple combinations, we selected 'pairs' as the basic measure of investigating multimorbidity. The 'pairs' provides the basis for clinically intuitive understanding of how two chronic disease pathways might combine together, but with six study chronic diseases chosen, the potential number of pairs could be 6x6=36. Therefore, six example pairs were chosen to represent the range of chronic diseases onsets from mid-life to old-age and included: (i) DM and HT; (ii) DM and CHD; (iii) DM and CKD; (iv) COPD and CHD; (v) COPD and CHF; and (vi) CHF and CKD. These multimorbid pairs were then compared to their respective 'index' conditions, for example, HT and DM multimorbidity was compared to the group with HT without DM (expressed as HT+ DM-) and DM without HT (DM+ HT-). Each multimorbid group and their respective 'index' conditions represent a within group (see **Table 1** for annotation of all study defined groups) and separate clinical hypothesis of the association between multimorbidity and healthcare outcomes. In addition to age and gender data available from the general practice records, and the Index of Multiple Deprivation (IMD) was used as a measure of socio-economic status. The IMD is a measure of multiple deprivation at the small area level.[15] Based on Census data the score combines a number of indicators, including economic, social and housing issues, into a single deprivation score for each small area in England.

Healthcare transitions data: A&E episodes and hospital admissions

Using the unique NHS Number allocated to an individual patient, a dataset was created linking their clinical data from general practice to any other information such as A&E attendance and hospital admissions (planned and unplanned) for the time period 1st January 2007 to 31st December 2009. The total number of attendances in the study time period for each A&E type including minor injury units and walk-in centres were included. Whilst there are a number of hospital providers within the region, the single major provider of emergency and acute hospital services for the city is the University Hospital of North Staffordshire (UHNS) NHS Trust. Hospital admissions were based on Hospital Episode Statistics (HES), which contain records for all NHS patients admitted to English hospitals in each financial year. These A&E and hospital data are means by which Primary Care (PCT) Commissioners arrange payment from the purchaser to the acute hospital Trust provider.[16] Linking these clinical databases make it possible to track healthcare patterns of individual patients. We used these data therefore to establish the

natural history of patients with multimorbidity and transitions across the A&E and hospital interfaces.

Healthcare transitions cost

For each transition activity, the allocated Healthcare Resource Group (HRG) was used as a measure of cost for an A&E episode or a hospital admission in the 3-year time-period. A HRG is a group of clinically similar treatments and care that require similar levels of healthcare resource. It allows commissioners to understand their activity in terms of the types of patients they care for and the treatments they undertake.[17,18] HRGs are currently used as a means of determining cost for individual patients in each financial year, depending on their healthcare use. From the individual-level HRG cost data for A&E episode or hospital admission, data was aggregated to the population-level costs for the specified multimorbidity groups for the whole of the 3-year time-period. Individual-level data were anonymised by the Public Health Intelligence Team and subsequently linked for analyses using study identifier by the project team, and provision of the anonymous data was made under existing service agreements.

Analyses

The multimorbidity populations are described by age bands (40-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, 90 years and over), gender and deprivation. The IMD score for the study population was summarised into quartiles ranging from quartile 1 (least deprived) to quartile 4 (most deprived).

Interface transitions for the six multimorbid groups and their respective index conditions were defined as follows. A&E transitions were first summarised as at least one episode in any one of the 3 years, and so does not include multiple episodes within the same year. A similar approach was used for summarising the hospital admissions. Chi square tests were used to assess trends in the association between study defined groups and recurrent A&E episodes and hospital admissions (defined as at least one in each of the 3 years). These data are then presented as counts measured from 0 (no episodes or admissions), 1 (one episode in any one of the 3 years), 2 (two episodes in any two of the 3 years), and 3 (at least one episode in all 3 years). ANOVA and ANCOVA with actual age, gender and IMD as covariates were used to estimate the significance of mean differences of number of A&E episodes, hospital admissions and costs, within each of

the multimorbid groups, comparing the pairs of diseases to their respective index diseases.

Total costs for the study time period were estimated for each individual patient who had any A&E episode or hospital admissions, and here the total costs relate to all A&E episodes and hospital admissions over the 3 year time-period. Using linear regression methods, the difference in total cost per patient over the 3 years for each multimorbid group was compared to the respective index conditions was assessed, adjusting for age, gender and deprivation. Within each of the six multimorbid groups, the regression coefficient was tested for significance differences from their respective reference category with cost allocation as zero (0).

Results

From a study population of 60,660 patients aged 40 years and over on specific chronic disease registers in a 3-year time-period, there were 9735 patients with HT and DM (16%), 3574 with DM and CHD (6%), 2894 with DM and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Socio-demographic characteristics of multimorbid pairs

Multimorbid pairs, which included DM and HT or CHD, showed age-related differences (**Table 2**). Within the DM and CKD multimorbid group, there was a higher proportion of older patients aged 70 years and over (51%), than within the DM and CHD group or the HT and DM multimorbid group. There were more women (64%) than men within the DM and CKD group, than the other two DM multimorbid groups, but the deprivation distributions were similar. Within the COPD and CHF multimorbid groups, there was a higher proportion of older patients aged 70 years and over (75%), compared to COPD and CHD, but within the COPD and CHD group there were more men (62%) than women. The CHF and CKD multimorbid group had the highest proportion who were aged 80 years and over (50%), and this group had more women than men.

Multimorbidity transitions across accident & emergency interface

Patients with HT and DM had the highest proportion without an A&E episode in the 3-year time-period (63%), but the patients with CKD and CHF had the lowest proportion without an A&E episode in the 3-year time-period (33%) (**Table 3**). The same figures for

other multimorbid groups were as follows: DM & CHD 52%; DM & CKD 51%; COPD & CHD 44%; and CHF & COPD 42%.

The proportion of patients with recurrent A&E episodes (defined as at least one episode in each of the 3 years) for multimorbid groups was as follows: HT and DM 2%, DM & CHD 4%, DM & CKD 3%, COPD & CHD 5%, CHF & COPD 7% and CKD & CHF 6%. These associations and increase across the groups was even more evident for patients who had had an A&E episode in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and recurrent A&E episodes (p<0.001).

Multimorbidity transitions across hospital admission interface

Patients with HT and DM had the highest proportion without a hospital admission in the 3-year time-period (49%), but the patients with CKD and CHF had the lowest proportion without a hospital admission in the 3-year time-period (21%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 39%; DM & CKD 37%; COPD & CHD 31%; and CHF & COPD 28%.

The proportion of patients with recurrent hospital admissions (defined as at least one in each of the 3 years) for multimorbid groups was as follows: HT and DM 6%; DM & CHD 10%; DM & CKD 10%; COPD & CHD 12%; CHF & COPD 13%; and CKD & CHF 13%. These associations and increase across the groups was even more evident for patients who had had a hospital admission in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index conditions, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission (p<0.001).

Health care costs at the accident & emergency transition

Patients with HT and DM had the lowest mean A&E costs in the 3-year time-period (total £69), but the highest figure was for patients with CHF and COPD or CKD (around £166) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £104; DM & CKD £105; COPD & CHD £138; and CHF & COPD £164.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher A&E costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two

notable groups. The A&E costs were £13 lower for the index CHD group compared to index COPD group, and £31 lower for index CKD group than the CHF group (**Table 3**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher A&E costs (p<0.001).

Healthcare costs at the hospital admission transition

Patients with HT and DM had the lowest mean hospital admissions costs in the 3-year time-period (total £2289), but patients with CHF and CKD had the highest costs (£5344) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £3372; DM & CKD £3642; COPD & CHD £3992; and CHF & COPD £4901.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher hospital admission costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The hospital admission costs were £152 lower for the index CHD group compared to index COPD group, and £629 lower for index CKD group than the CHF group (**Table 4**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission costs (p<0.001).

The six multimorbid groups were selected on the basis of age-related onsets. However, comparing the findings for the six multimorbid pairs, after age adjustment, also showed that these groups can be placed into an order of an increasing association between the 'severity' of multimorbid pair and the likelihood of A&E episodes and associated costs, or hospital admissions and associated costs over the 3-year time-period. The 'severity' of health care impact can be ordered as follows: DM and HT ('low severity'), DM and CHD, DM and CKD, COPD and CHD, CHF & COPD, and CHF and CKD ('high severity') (**Tables 3 and 4**).

Discussion

Our large scale study in a chronic disease population showed that patients with specific multimorbidity pairs had distinct variations in healthcare transitions and in the associated healthcare costs. Whilst age is a specific indicator for the type of multiple chronic disease, adjustment for socio-demographic factors, still showed that specific

multimorbidity pairs were associated with higher number of healthcare transitions compared to their respective index groups. Furthermore, these multimorbidity associations suggest that they can be ordered into a 'severity of healthcare impact', after adjusting for age. In this spectrum, multimorbidity such as hypertension and diabetes represents one end of the healthcare cost spectrum and chronic heart failure and chronic kidney disease representing the higher and most costly end of healthcare impact.

The implications of this multimorbidity study covering a 3-year time-period relates to the number of transitions and costs of transitions. The study shows that patients with specific multimorbidity has higher number of annual A&E episodes or hospital admissions and costs, which means that this provides a potential mechanism for targeting patients for intervention across the healthcare interfaces. Since this information could potentially be linked across the interface, it also provides the basis for intervention once initial transitions have occurred to prevent future unnecessary transitions from general practice to A&E or hospital admission.

The study was based on large scale data available from 53 general practices in one of the most deprived regions in England and over a long term time period of 3 years. The current national quality improvements approaches have been based on establishing chronic disease registers in clinical practice and aim at improving care for the individual patient.[12,19] However such registers also provide the basis for defining population-level impacts and for providing the integration between public health prevention (general practice or local area) and individual-level care. The definition of multimorbidity, focusing on 'pairs' also means that it allows easier interpretation of the current individual pathways of care and begins to provide insight into how these might be integrated. For example, hypertension, diabetes and coronary heart disease are often jointly managed in general practice, but in healthcare transitions, specialist care could be delivered by nephrology (hypertension), diabetes or cardiology. However in severe chronic disease states, such as COPD, CHF and CKD, which are often jointly managed between general practice and hospital-based care, such 'multimorbidity pair' approach allows for the integration of care for high cost patients who may be cared for by several healthcare teams in different individual care pathways.

Whilst this was a large scale study, the cross-sectional findings relate to one region of England. The patterns of transitions may differ in other regions, especially as services moved to different integrated models, but the relative associations for multimorbid

groups compared to the index groups provide the best available estimates on the impact on transitions and costs. These cost estimations and relative are conservative as the reference comparison groups had one of the two multimorbid conditions, whereas a non-index reference group without either pair condition would have magnified the relative cost differences. Whilst new integrated models of care are developing[20], such care will still need to differentiate between the acute health needs of the patient with a chronic disease addressed by specialist intervention, and the chronic health needs and monitoring that will be addressed by general practice and community teams. The study definitions also focused on pairs of conditions but all groups were not exclusive, and there was some overlap. For example diabetes was paired with hypertension, coronary heart disease and chronic kidney disease, which indicates an overlap, but these results showed that different pairs with the same index condition (e.g. diabetes) have distinct associations with healthcare transitions and costs.

The chronic disease registers from general practice were part of local and national initiatives, and such data are now used widely in performance and payment reporting, and healthcare studies.[19] The healthcare transition data also are part of national performance and payment reporting, and have also been used in healthcare studies. The recording of these transition episodes (A&E or hospital admission) will be accurate as the healthcare costs are based on the HRG allocated to each individual patient, and which is part of the cost transaction process between healthcare commissioner (PCT) and the provider (hospital). Furthermore the transitions data and cost data are part of national validation processes.[16,21] In this study, the primary objective was to test the clinical hypothesis that different multimorbidity pairs showed variations in overall healthcare transitions, and therefore does not include the attempt to characterise the precise nature of each transition episode. The estimated costs for these patient populations are also an under-estimate since they do not include ongoing healthcare costs in general practice and community care.

Previously there have been few studies on multimorbidity and costs in specific settings[22,23], but there is a lack of healthcare transitions data, and the hypothesis that a study of specific ‘disease pairs’ may provide insight into healthcare presentation and costs has not been previously tested. Much of the current multimorbidity research has focused on the ‘burden’ as exemplified by the number of conditions that patient’s experience, but the key limitation with the ‘counting’ approach is the lack of differentiation of how it links into the current individual disease-designed pathways.

Arguably, it is better conceptualise this issue into 'which pairs' and link it practically to the individual disease pathways which have been devised in terms of chronic disease model of care.[24] Notably the notion of chronic disease and depression has been well constructed in the psychiatric field.[25] This 'disease pair' approach provides a simple and clinically intuitively approach that can be readily used in actual clinical practice, and a means by which local policy decisions can incorporate estimated costs for healthcare transitions.

This cross-sectional study provides the basis for the innovative linking of data, and understanding the healthcare 'journey' for the patient with different chronic diseases. Further studies would address issues such as multiple healthcare transitions, combining different interfaces (for example, identifying patients who attend A&E regularly and are admitted regularly) and the underlying and precise clinical reasons for the healthcare costs. For example, healthcare transitions may cover community care, and wider transitions could include social care. The associations shown in this study also need to be complemented by the temporal investigation between chronic disease pairs and subsequent impact on the time between health care transitions.

In conclusion, our study showed that specific multimorbid pairs compared to their index morbidity, indicated the level of transitions across healthcare interfaces and the associated total healthcare costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

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Table 1: Study groups

Annotation	Study groups
HT+ DM-	Hypertension *without* diabetes mellitus
DM+ HT-	Diabetes mellitus *without* hypertension
HT & DM	Multimorbidity of hypertension *and* diabetes mellitus
DM+ CHD-	Diabetes mellitus *without* coronary heart disease
CHD+ DM-	Coronary heart disease *without* diabetes mellitus
DM & CHD	Multimorbidity of diabetes mellitus *and* coronary heart disease
DM+ CKD-	Diabetes mellitus *without* chronic kidney disease
CKD+ DM-	Chronic kidney disease *without* diabetes mellitus
DM & CKD	Multimorbidity of diabetes mellitus *and* chronic kidney disease
COPD+ CHD-	Chronic obstructive pulmonary disease *without* coronary heart disease
CHD+ COPD-	Coronary heart disease *without* chronic obstructive pulmonary disease
COPD & CHD	Multimorbidity of chronic obstructive pulmonary disease *and* coronary heart disease
COPD+ CHF-	Chronic obstructive pulmonary disease *without* chronic heart failure
CHF+ COPD-	Chronic heart failure *without* chronic obstructive pulmonary disease
CHF & COPD	Multimorbidity of chronic heart failure *and* chronic obstructive pulmonary disease
CHF+ CKD-	Chronic heart failure *without* chronic kidney disease
CKD+ CHF-	Chronic kidney disease *without* chronic heart failure
CKD & CHF	Multimorbidity of chronic kidney disease *and* chronic heart failure

Table 2: Socio-demographic characteristics of the multimorbid study pairs

Groups	HT & DM *No (%)* (n=9735)	DM & CHD *No (%)* (n=3574)	DM & CKD *No (%)* (n=2894)	CHD & COPD *No (%)* (n=1855)	CHF & COPD *No (%)* (n=754)	CHF & CKD *No (%)* (n=1425)
40-49 years	866 (8.9)	152 (4.2)	48 (1.7)	22 (1.2)	4 (0.5)	6 (0.4)
50-59 years	2043 (21.0)	533 (14.9)	227 (7.8)	179 (9.6)	42 (5.5)	49 (3.4)
60-69 years	2866 (29.4)	1067 (29.8)	645 (22.3)	499 (26.8)	140 (18.6)	177 (12.4)
70-79 years	2686 (27.6)	1219 (34.1)	1200 (41.3)	710 (38.3)	298 (39.3)	488 (34.2)
80-89 years	1152 (11.9)	552 (15.5)	691 (24.0)	409 (22.1)	236 (31.6)	594 (41.9)
90 years and over	122 (1.3)	51 (1.5)	83 (2.9)	36 (2.0)	34 (4.5)	111 (7.7)
Men	5016 (51.5)	2162 (60.4)	1055 (36.4)	1152 (62.1)	427 (56.4)	549 (38.5)
Women	4719 (48.5)	1412 (39.6)	1839 (63.6)	703 (37.9)	327 (43.6)	876 (61.5)
Quartile 1* Least deprived	2044 (21.1)	691 (19.5)	596 (20.7)	249 (13.5)	109 (14.5)	300 (21.1)
Quartile 2	2335 (24.1)	785 (22.1)	652 (22.6)	428 (23.2)	171 (22.8)	340 (23.9)
Quartile 3	2541 (26.2)	934 (26.3)	801 (28.9)	527 (28.5)	205 (27.3)	401 (28.2)
Quartile 4 Most deprived	2768 (28.6)	1142 (32.2)	831 (28.9)	644 (34.8)	265 (35.3)	379 (26.7)

**Deprivation measured using the Index of Multiple Deprivation; HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 3: Multimorbidity transitions across A&E and hospital admission interface over 3-years

Study Groups†	A & E episodes				Hospital admissions			
	0	1	2	3	0	1	2	3
	No (%)	*No (%)*	*No (%)*	No (%)	*No (%)*	*No (%)*	*No (%)*	*No (%)*
HT+ DM-	26019 (68.6)	8903 (23.5)	2466 (6.5)	548 (1.4)	21957 (54.0)	10443 (27.5)	4223 (11.1)	1313 (3.5)
DM+ HT-	2733 (63.2)	1154 (26.4)	372 (8.4)	96 (2.1)	2343 (54.0)	1192 (27.5)	601 (13.8)	204 (4.7)
HT & DM	6168 (63.4)	2581 (26.5)	776 (8.0)	210 (2.2)	4800 (49.3)	2888 (29.7)	1456 (15.0)	591 (6.1)
DM+ CHD-	7048 (67.1)	2580 (24.6)	703 (6.7)	170 (1.6)	5766 (54.9)	2993 (28.2)	1403 (12.7)	490 (4.2)
CHD+ DM-	6223 (57.6)	3175 (29.4)	1133 (10.5)	276 (2.6)	4842 (44.8)	3482 (32.2)	1813 (16.8)	670 (6.2)
DM & CHD	1863 (52.1)	1145 (32.0)	436 (12.2)	130 (3.6)	1377 (38.5)	1123 (31.4)	721 (20.2)	353 (9.9)
DM+ CKD-	7440 (66.5)	2761 (24.7)	775 (6.9)	205 (1.8)	6083 (54.4)	3142 (28.1)	1438 (12.9)	518 (4.6)
CKD+ DM-	5137 (57.3)	2733 (30.5)	893 (10.0)	195 (2.2)	3923 (43.8)	3056 (34.1)	1502 (16.8)	477 (5.3)
DM & CKD	1471 (50.8)	964 (33.3)	364 (12.6)	95 (3.3)	1060 (36.6)	938 (32.4)	619 (21.4)	277 (9.6)
COPD+ CHD-	3013 (56.8)	1568 (29.6)	546 (10.3)	177 (3.3)	2443 (46.1)	1665 (31.4)	843 (15.9)	353 (6.7)
CHD+ COPD-	7267 (58.0)	3689 (29.5)	1261 (10.1)	309 (2.5)	5641 (45.0)	3973 (31.7)	2108 (16.8)	804 (6.4)
COPD & CHD	819 (44.2)	631 (34.0)	308 (16.6)	97 (5.2)	578 (31.2)	632 (34.1)	426 (23.0)	219 (11.8)

COPD+ CHF-	3519 (54.9)	1940 (30.3)	723 (11.3)	223 (3.5)	2810 (43.9)	2018 (31.5)	1102 (17.2)	475 (7.4)
CHF+ COPD-	1346 (46.7)	990 (34.3)	440 (15.3)	108 (3.7)	978 (33.9)	996 (34.5)	645 (22.4)	265 (9.2)
CHF & COPD	313 (41.5)	259 (34.4)	131 (17.4)	51 (6.8)	211 (28.0)	279 (37.0)	167 (22.1)	97 (12.9)
CHF+ CKD-	1173 (53.0)	665 (30.0)	295 (13.3)	80 (3.6)	884 (39.9)	737 (33.3)	414 (18.7)	178 (8.0)
CKD+ CHF-	6122 (58.7)	3113 (29.9)	981 (9.4)	211 (2.0)	4678 (44.9)	3456 (33.1)	1723 (16.5)	570 (5.5)
CKD & CHF	481 (33.4)	595 (41.3)	284 (19.7)	80 (5.6)	305 (21.4)	538 (37.8)	398 (27.9)	184 (12.9)

† *minus sign indicates absence of disease and positive sign indicates presence, HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 4: Multimorbidity transitions across A&E episodes and hospital admissions and associated costs over 3-years

Study Groups	3-year AE £ costs Mean (SD)	Adjusted £ Regression Estimates (SE)	*p*-value	3-year IP £ costs Mean (SD)	Adjusted £ Regression Estimates (SE)	*p*-value
HT+ DM-	55 (132)	0		1647 (4085)	0	
DM+ HT-	69 (162)	20 (2)	<.001	2061 (4490)	595 (68)	<.001
HT & DM	69 (152)	14 (2)	<.001	2289 (4585)	607 (48)	<.001
DM+ CHD-	57 (124)	0		1825 (3977)	0	
CHD+ DM-	84 (175)	22 (2)	<.001	2512 (5825)	431 (73)	<.001
DM & CHD	104 (219)	42 (3)	<.001	3372 (5789)	1270 (101)	<.001
DM+ CKD-	60 (143)	0		1850 (3996)	0	
CKD+ DM-	80 (144)	4 (2)	0.14	2559 (4380)	403 (73)	<.001
DM & CKD	105 (190)	30 (3)	<.001	3642 (6063)	1480 (97)	<.001
COPD+ CHD-	96 (214)	0		2642 (4814)	0	
CHD+ COPD-	81 (180)	-13 (4)	<.001	2537 (5812)	-152 (92)	.097
COPD & CHD	138 (219)	40 (5)	<.001	3992 (5775)	1158 (151)	<.001
COPD+ CHF-	100 (211)	0		2769 (4925)	0	
CHF+ COPD-	120 (192)	17 (5)	<.001	3877 (5732)	904 (125)	<.001
CHF & COPD	166 (242)	64 (8)	<.001	4901 (6199)	1954 (206)	<.001
CHF+ CKD-	108 (176)	0		3282 (4880)	0	
CKD+ CHF-	75 (139)	-31 (4)	<.001	2477 (4404)	-629 (114)	<.001
CKD & CHF	164 (238)	52 (5)	<.001	5344 (6907)	2116 (163)	<.001

DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease HT=hypertension,

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Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

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Title: Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

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Abstract

Objective: To investigate multimorbidity transitions from general practice populations across healthcare interfaces and the associated healthcare costs.

Design: Clinical-linkage database study.

Setting: Population (N=60,660) aged 40 years and over registered with 53 general practices in Stoke-on-Trent.

Participants: Population with six specified multimorbidity pairs were identified based on hypertension, diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and chronic kidney disease (CKD).

Main outcomes measures: Chronic disease registers were linked to accident and emergency (A&E) and hospital admissions for a 3-year time-period (2007-2009), and associated costs measured by Healthcare Resource Groups. Associations between multimorbid groups and direct healthcare costs were compared to their respective single disease groups using linear regression methods, adjusting for age, gender and deprivation.

Results: In the study population, there were 9735 patients with hypertension and diabetes (16%), 3574 with diabetes and CHD (6%), 2894 with diabetes and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Transition defined as at least one episode in each of the three year time-period, were as follows: patients with hypertension and DM had the fewest transitions in the 3-year time-period (37% A&E episode and 51% hospital admission), but CHF and CKD has the most transitions (67% A&E episode and 79% hospital admission).

The average 3-year total costs per multimorbid patient for A&E episodes ranged from £69 to £166 and for hospital admissions ranged from between £2289 to £5344. The adjusted costs were significantly higher for all six multimorbid groups compared to their respective single disease groups.

Conclusions: Specific common multimorbid pairs are associated with higher healthcare transitions and differential costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of integrated care.

Article summary

Article focus

- In the population there are large numbers of people who suffer with two or multiple chronic diseases at the same time.
- Most of the current evidence has focused on the impact of multimorbidity on health status and very few have investigated the transitions across healthcare and the associated costs.
- Whilst individual chronic diseases have been shown to be associated with high health care costs, whether specific multimorbid combinations have differential healthcare transitions and healthcare costs is unknown.

Key messages

- Specific multimorbid pairs are associated with different levels of healthcare transitions and costs relating to accident and emergency and to hospital admissions.
- Chronic disease pairs indicate the population level multimorbidity 'severity' as indicated by transitions and costs, with a range from diabetes and hypertension ('low severity'), diabetes and heart disease, diabetes and chronic kidney disease, COPD and heart disease, heart failure & COPD, to heart failure and chronic kidney disease ('high severity').
- Identification of multimorbidity type and linkage of information across healthcare interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

Strengths and limitations of this study

- The study was based on large scale data linking chronic disease registers from general practices to A&E episodes and hospital admissions
- The study highlights the innovative potential of linkage data between healthcare interfaces to inform healthcare delivery
- The study uses a specific, but a limited number of common chronic diseases to illustrate the approach to using linked data within a single large region of the UK

Background

Multimorbidity is an individual's experience of two or more illnesses at the same time. In ageing populations the numbers of people with such multimorbidity will increase substantially, and it is estimated that there are up to 20% of the British population (4 million people) who may experience such multimorbidity[1], with a projected further increase of 37% in the England & Wales population aged 50 years and over by the year 2031. This means that the current focus of health care delivery on specific disease-focus outcomes will have to be complemented by a Public Health priority focusing on multimorbidity in older populations.

Current evidence on multiple disease in the same person has shown that this is a common problem, which has high impact on an individual's health and on the use of health care resources.[2,3,4] However, people may also experience transitions i.e. health care changes from general practice to different healthcare interfaces such as Accident and Emergency or hospital care, especially as delivery of chronic disease is orientated around individual healthcare pathways. Once a person experiences a number of different diseases, the issue then becomes how the person interacts with different healthcare interfaces. Current research has shown that in specific settings, such as general practice[5] or hospitals, multimorbidity is common in the encounters that are present in the disease-care pathways.[6,7] However, there is little empirical data on how multimorbidity influences transitions across different healthcare interfaces and whether specific multimorbidity combinations are more likely to be associated with higher healthcare presentations, such as Accident and Emergency (A&E) episodes or hospital admissions. Routine coding of such patients encounters now occurs in clinical practice, A&E and hospitals, and technological developments allow the linkage of clinical information across these interfaces.[8] These developments allow for the potential for targeted prevention and new models of healthcare interventions for patients who experience multiple chronic diseases at the same time.

The other key area of focus is how cost-effective care pathways can be developed. By understanding how multimorbidity influences interface presentation and the associated healthcare costs, it can be explored as to whether healthcare cost can be 'benchmarked' for specific conditions and combinations of conditions.[9] Currently much of the chronic disease healthcare delivery pathways has aligned along single-disease lines, for example diabetes, chronic obstructive airways disease or heart failure. So the potential range of multimorbidity model of care could range from joint clinics (e.g. diabetes and

renal) to the holistic clinical assessment conducted by elderly care physicians.[10,11] However, one could argue the next simple step from single disease pathway care to a multimorbidity approach, is understanding pair combinations which link to at least two individual disease care pathways, and which we use in this study by selecting common chronic diseases in the older population. Using a large linkage dataset we investigated the clinical hypothesis as to whether specific chronic disease multimorbidity pairs are associated with differences in health care transitions and associated healthcare costs, and compared to populations with only one of the respective matched conditions.

Methods

Design

The design of the study was a cross-sectional clinical linkage study of the population aged 40 years and over on chronic disease registers to transition data on A&E episode or hospital admission in a 3-year time-period (1st January 2007 to 31st December 2009).

Setting

The setting is an urban population of around 240,000 which focuses around the city of Stoke-on-Trent, which is one of the most deprived in England & Wales and has some of the highest levels of chronic disease prevalence and over half of areas are in the most deprived 20% in England.[12]

Clinical linkage datasets

Chronic disease registers

The local Primary Care Trust oversees 53 general practices and all practices have been participating in a national and local quality improvement framework[13] for specific chronic diseases, and in recording clinical data through regular data audits and checks. For specified conditions, using the Read Code classification[14], General Practitioners (GPs) and their teams had recorded clinical data on disease registers for their population. These practices contributed to the construction of a clinical database, which for this study covers a 3-year time-period. From this database, all adults on chronic disease registers for the following six conditions were identified: hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and chronic kidney disease (CKD).

Multimorbidity definitions

Whilst multimorbidity could be characterised for the study as any number or multiple combinations, we selected 'pairs' as the basic measure of investigating multimorbidity. The 'pairs' provides the basis for clinically intuitive understanding of how two chronic disease pathways might combine together, but with six study chronic diseases chosen, the potential number of pairs could be 6x6=36. Therefore, six example pairs were chosen to represent the range of chronic diseases onsets from mid-life to old-age and included: (i) DM and HT; (ii) DM and CHD; (iii) DM and CKD; (iv) COPD and CHD; (v) COPD and CHF; and (vi) CHF and CKD. These multimorbid pairs were then compared to their respective 'index' conditions, for example, HT and DM multimorbidity was compared to the group with HT without DM (expressed as HT+ DM-) and DM without HT (DM+ HT-). Each multimorbid group and their respective 'index' conditions represent a within group (see **Table 1** for annotation of all study defined groups) and separate clinical hypothesis of the association between multimorbidity and healthcare outcomes. Whilst this approach means that there might be overlap between multimorbid pair groups, each study group had been selected by common conditions of interest, and not in relation to other multimorbidity that might be present or absent.

In addition to age and gender data available from the general practice records, and the Index of Multiple Deprivation (IMD) was used as a measure of socio-economic status. The IMD is a measure of multiple deprivation at the small area level.[15] Based on Census data the score combines a number of indicators, including economic, social and housing issues, into a single deprivation score for each small area in England.

Healthcare transitions data: A&E episodes and hospital admissions

Using the unique NHS Number allocated to an individual patient, a dataset was created linking their clinical data from general practice to any other information such as A&E attendance and hospital admissions (planned and unplanned) for the time period 1st January 2007 to 31st December 2009. The total number of attendances in the study time period for each A&E type including minor injury units and walk-in centres were included. Whilst there are a number of hospital providers within the region, the single major provider of emergency and acute hospital services for the city is the University Hospital of North Staffordshire (UHNS) NHS Trust. Hospital admissions were based on Hospital Episode Statistics (HES), which contain records for all NHS patients admitted to any English hospitals in each financial year. These A&E and hospital data are means by

which Primary Care (PCT) Commissioners arrange payment from the purchaser to the acute hospital Trust provider.[16] Linking these clinical databases make it possible to track healthcare patterns of individual patients. We used these data therefore to establish the natural history of patients with multimorbidity and transitions across the A&E and hospital interfaces.

Healthcare transitions cost

For each transition activity, the allocated Healthcare Resource Group (HRG) was used as a measure of cost for an A&E episode or a hospital admission in the 3-year time-period. A HRG is a group of clinically similar treatments and care that require similar levels of healthcare resource. It allows commissioners to understand their activity in terms of the types of patients they care for and the treatments they undertake.[17,18] HRGs are currently used as a means of determining cost for individual patients in each financial year, depending on their healthcare use. From the individual-level HRG cost data for A&E episode or hospital admission, data was aggregated to the population-level costs for the specified multimorbidity groups for the whole of the 3-year time-period. Individual-level data were anonymised by the Public Health Intelligence Team and subsequently linked for analyses using study identifier by the project team, and provision of the anonymous data was made under existing service agreements.

Analyses

The multimorbidity populations are described by age bands (40-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, 90 years and over), gender and deprivation. The IMD score for the study population was summarised into quartiles ranging from quartile 1 (least deprived) to quartile 4 (most deprived). The socio-demographic prevalence for the study multimorbidity pairs and respective index conditions, including the population without index condition was also estimated and information is given in **Supplementary tables 1 to 3**.

Interface transitions for the six multimorbid groups and their respective index conditions were defined as follows. A&E transitions were first summarised as at least one episode in any one of the 3 years, and so does not include multiple episodes within the same year. A similar approach was used for summarising the hospital admissions. Chi square tests were used to assess trends in the association between study defined groups and recurrent A&E episodes and hospital admissions (defined as at least one in each of the

3 years). These data are then presented as counts measured from 0 (no episodes or admissions), 1 (one episode in any one of the 3 years), 2 (two episodes in any two of the 3 years), and 3 (at least one episode in all 3 years). ANOVA and ANCOVA with actual age, gender and IMD as covariates were used to estimate the significance of mean differences of number of A&E episodes, hospital admissions and costs, within each of the multimorbid groups, comparing the pairs of diseases to their respective index diseases.

Total costs for the study time period were estimated for each individual patient who had any A&E episode or hospital admissions, and here the total costs relate to all A&E episodes and hospital admissions over the 3 year time-period. Using linear regression methods, the difference in total cost per patient over the 3 years for each multimorbid group was compared to the respective index conditions was assessed, adjusting for age, gender and deprivation. Within each of the six multimorbid groups, the regression coefficient was tested for significance differences from their respective reference category with cost allocation as zero (0).

Results

From a study population of 60,660 patients aged 40 years and over on specific chronic disease registers in a 3-year time-period, there were 9735 patients with HT and DM (16%), 3574 with DM and CHD (6%), 2894 with DM and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%). The socio-demographic prevalence figures for the multimorbidity pair groups and comparator groups are given in **Supplementary Tables 1 to 3**.

Socio-demographic characteristics of multimorbid pairs

Multimorbid pairs, which included DM and HT or CHD, showed age-related differences (**Table 2**). Within the DM and CKD multimorbid group, there was a higher proportion of older patients aged 70 years and over (51%), than within the DM and CHD group or the HT and DM multimorbid group. There were more women (64%) than men within the DM and CKD group, than the other two DM multimorbid groups, but the deprivation distributions were similar. Within the COPD and CHF multimorbid groups, there was a higher proportion of older patients aged 70 years and over (75%), compared to COPD and CHD, but within the COPD and CHD group there were more men (62%) than

women. The CHF and CKD multimorbid group had the highest proportion who were aged 80 years and over (50%), and this group had more women than men.

Multimorbidity transitions across accident & emergency interface

Patients with HT and DM had the highest proportion without an A&E episode in the 3-year time-period (63%), but the patients with CKD and CHF had the lowest proportion without an A&E episode in the 3-year time-period (33%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 52%; DM & CKD 51%; COPD & CHD 44%; and CHF & COPD 42%.

The proportion of patients with recurrent A&E episodes (defined as at least one episode in each of the 3 years) for multimorbid groups was as follows: HT and DM 2%, DM & CHD 4%, DM & CKD 3%, COPD & CHD 5%, CHF & COPD 7% and CKD & CHF 6%. These associations and increase across the groups was even more evident for patients who had had an A&E episode in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and recurrent A&E episodes (p<0.001).

Multimorbidity transitions across hospital admission interface

Patients with HT and DM had the highest proportion without a hospital admission in the 3-year time-period (49%), but the patients with CKD and CHF had the lowest proportion without a hospital admission in the 3-year time-period (21%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 39%; DM & CKD 37%; COPD & CHD 31%; and CHF & COPD 28%.

The proportion of patients with recurrent hospital admissions (defined as at least one in each of the 3 years) for multimorbid groups was as follows: HT and DM 6%; DM & CHD 10%; DM & CKD 10%; COPD & CHD 12%; CHF & COPD 13%; and CKD & CHF 13%. These associations and increase across the groups was even more evident for patients who had had a hospital admission in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index conditions, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission (p<0.001).

Health care costs at the accident & emergency transition

Patients with HT and DM had the lowest mean A&E costs in the 3-year time-period (total £69), but the highest figure was for patients with CHF and COPD or CKD (around £166) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £104; DM & CKD £105; COPD & CHD £138; and CHF & COPD £164.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher A&E costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The A&E costs were £13 lower for the index CHD group compared to index COPD group, and £31 lower for index CKD group than the CHF group (**Table 3**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher A&E costs (p<0.001).

Healthcare costs at the hospital admission transition

Patients with HT and DM had the lowest mean hospital admissions costs in the 3-year time-period (total £2289), but patients with CHF and CKD had the highest costs (£5344) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £3372; DM & CKD £3642; COPD & CHD £3992; and CHF & COPD £4901.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher hospital admission costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The hospital admission costs were £152 lower for the index CHD group compared to index COPD group, and £629 lower for index CKD group than the CHF group (**Table 4**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission costs (p<0.001).

The six multimorbid groups were selected on the basis of age-related onsets. However, comparing the findings for the six multimorbid pairs, after age adjustment, also showed that these groups can be placed into an order of an increasing association between the 'severity' of multimorbid pair and the likelihood of A&E episodes and associated costs, or hospital admissions and associated costs over the 3-year time-period. The 'severity' of health care impact can be ordered as follows: DM and HT ('low severity'), DM and CHD,

DM and CKD, COPD and CHD, CHF & COPD, and CHF and CKD ('high severity') (**Tables 3 and 4**).

Discussion

Our large scale study in a chronic disease population showed that patients with specific multimorbidity pairs had distinct variations in healthcare transitions and in the associated healthcare costs. Whilst age is a specific indicator for the type of multiple chronic disease, adjustment for socio-demographic factors, still showed that specific multimorbidity pairs were associated with higher number of healthcare transitions compared to their respective index groups. Furthermore, these multimorbidity associations suggest that they can be ordered into a 'severity of healthcare impact', after adjusting for age. In this spectrum, multimorbidity such as hypertension and diabetes represents one end of the healthcare cost spectrum and chronic heart failure and chronic kidney disease representing the higher and most costly end of healthcare impact.

The implications of this multimorbidity study covering a 3-year time-period relates to the number of transitions and costs of transitions. The study shows that patients with specific multimorbidity has higher number of annual A&E episodes or hospital admissions and costs, which means that this provides a potential mechanism for targeting patients for intervention across the healthcare interfaces. Since this information could potentially be linked across the interface, it also provides the basis for intervention once initial transitions have occurred to prevent future unnecessary transitions from general practice to A&E or hospital admission.

The study was based on large scale data available from 53 general practices in one of the most deprived regions in England and over a long term time period of 3 years. The current national quality improvements approaches have been based on establishing chronic disease registers in clinical practice and aim at improving care for the individual patient.[12,19] However such registers also provide the basis for defining population-level impacts and for providing the integration between public health prevention (general practice or local area) and individual-level care. The definition of multimorbidity, focusing on 'pairs' also means that it allows easier interpretation of the current individual pathways of care and begins to provide insight into how these might be integrated. For example, hypertension, diabetes and coronary heart disease are often jointly managed in general practice, but in healthcare transitions, specialist care could be delivered by

nephrology (hypertension), diabetes or cardiology. However in severe chronic disease states, such as COPD, CHF and CKD, which are often jointly managed between general practice and hospital-based care, such 'multimorbidity pair' approach allows for the integration of care for high cost patients who may be cared for by several healthcare teams in different individual care pathways.

Whilst this was a large scale study, the cross-sectional findings relate to one region of England. The patterns of transitions may differ in other regions, especially as services moved to different integrated models, but the relative associations for multimorbid groups compared to the index groups provide the best available estimates on the impact on transitions and costs. These cost estimations and relative are conservative as the reference comparison groups had one of the two multimorbid conditions, whereas a non-index reference group without either pair condition would have magnified the relative cost differences. Whilst new integrated models of care are developing[20], such care will still need to differentiate between the acute health needs of the patient with a chronic disease addressed by specialist intervention, and the chronic health needs and monitoring that will be addressed by general practice and community teams. The study definitions also focused on pairs of conditions but all groups were not exclusive, and there was some overlap. For example diabetes was paired with hypertension, coronary heart disease and chronic kidney disease, which indicates an overlap, but these results showed that different pairs with the same index condition (e.g. diabetes) have distinct associations with healthcare transitions and costs.

The chronic disease registers from general practice were part of local and national initiatives, and such data are now used widely in performance and payment reporting, and healthcare studies.[19] The healthcare transition data also are part of national performance and payment reporting, and have also been used in healthcare studies. The recording of these transition episodes (A&E or hospital admission) will be accurate as the healthcare costs are based on the HRG allocated to each individual patient, and which is part of the cost transaction process between healthcare commissioner (PCT) and the provider (hospital). Furthermore the transitions data and cost data are part of national validation processes.[16,21] In this study, the primary objective was to test the clinical hypothesis that different multimorbidity pairs showed variations in overall healthcare transitions, and therefore does not include the attempt to characterise the precise nature of each transition episode. The estimated costs for these patient

populations are also an under-estimate since they do not include ongoing healthcare costs in general practice and community care.

Previously there have been few studies on multimorbidity and costs in specific settings[22,23], but there is a lack of healthcare transitions data, and the hypothesis that a study of specific 'disease pairs' may provide insight into healthcare presentation and costs has not been previously tested. Much of the current multimorbidity research has focused on the 'burden' as exemplified by the number of conditions that patient's experience, but the key limitation with the 'counting' approach is the lack of differentiation of how it links into the current individual disease-designed pathways. Arguably, it is better conceptualise this issue into 'which pairs' and link it practically to the individual disease pathways which have been devised in terms of chronic disease model of care.[24] Notably the notion of chronic disease and depression has been well constructed in the psychiatric field.[25] This 'disease pair' approach provides a simple and clinically intuitively approach that can be readily used in actual clinical practice, and a means by which local policy decisions can incorporate estimated costs for healthcare transitions.

This cross-sectional study provides the basis for the innovative linking of data, and understanding the healthcare 'journey' for the patient with different chronic diseases. Further studies would address issues such as multiple healthcare transitions, combining different interfaces (for example, identifying patients who attend A&E regularly and are admitted regularly) and the underlying and precise clinical reasons for the healthcare costs. For example, healthcare transitions may cover community care, and wider transitions could include social care. The associations shown in this study also need to be complemented by the temporal investigation between chronic disease pairs and subsequent impact on the time between health care transitions.

In conclusion, our study showed that specific multimorbid pairs compared to their index morbidity, indicated the level of transitions across healthcare interfaces and the associated total healthcare costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

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Table 1: Study groups

Annotation	Study groups
HT+ DM-	Hypertension *without* diabetes mellitus
DM+ HT-	Diabetes mellitus *without* hypertension
HT & DM	Multimorbidity of hypertension *and* diabetes mellitus
DM+ CHD-	Diabetes mellitus *without* coronary heart disease
CHD+ DM-	Coronary heart disease *without* diabetes mellitus
DM & CHD	Multimorbidity of diabetes mellitus *and* coronary heart disease
DM+ CKD-	Diabetes mellitus *without* chronic kidney disease
CKD+ DM-	Chronic kidney disease *without* diabetes mellitus
DM & CKD	Multimorbidity of diabetes mellitus *and* chronic kidney disease
COPD+ CHD-	Chronic obstructive pulmonary disease *without* coronary heart disease
CHD+ COPD-	Coronary heart disease *without* chronic obstructive pulmonary disease
COPD & CHD	Multimorbidity of chronic obstructive pulmonary disease *and* coronary heart disease
COPD+ CHF-	Chronic obstructive pulmonary disease *without* chronic heart failure
CHF+ COPD-	Chronic heart failure *without* chronic obstructive pulmonary disease
CHF & COPD	Multimorbidity of chronic heart failure *and* chronic obstructive pulmonary disease
CHF+ CKD-	Chronic heart failure *without* chronic kidney disease
CKD+ CHF-	Chronic kidney disease *without* chronic heart failure
CKD & CHF	Multimorbidity of chronic kidney disease *and* chronic heart failure

Table 2: Socio-demographic characteristics of the multimorbid study pairs

Groups	HT & DM *No. (%)* (n=9735)	DM & CHD *No. (%)* (n=3574)	DM & CKD *No. (%)* (n=2894)	CHD & COPD *No. (%)* (n=1855)	CHF & COPD *No. (%)* (n=754)	CHF & CKD *No. (%)* (n=1425)
40-49 years	866 (8.9)	152 (4.2)	48 (1.7)	22 (1.2)	4 (0.5)	6 (0.4)
50-59 years	2043 (21.0)	533 (14.9)	227 (7.8)	179 (9.6)	42 (5.5)	49 (3.4)
60-69 years	2866 (29.4)	1067 (29.8)	645 (22.3)	499 (26.8)	140 (18.6)	177 (12.4)
70-79 years	2686 (27.6)	1219 (34.1)	1200 (41.3)	710 (38.3)	298 (39.3)	488 (34.2)
80-89 years	1152 (11.9)	552 (15.5)	691 (24.0)	409 (22.1)	236 (31.6)	594 (41.9)
90 years and over	122 (1.3)	51 (1.5)	83 (2.9)	36 (2.0)	34 (4.5)	111 (7.7)
Men	5016 (51.5)	2162 (60.4)	1055 (36.4)	1152 (62.1)	427 (56.4)	549 (38.5)
Women	4719 (48.5)	1412 (39.6)	1839 (63.6)	703 (37.9)	327 (43.6)	876 (61.5)
Quartile 1* Least deprived	2044 (21.1)	691 (19.5)	596 (20.7)	249 (13.5)	109 (14.5)	300 (21.1)
Quartile 2	2335 (24.1)	785 (22.1)	652 (22.6)	428 (23.2)	171 (22.8)	340 (23.9)
Quartile 3	2541 (26.2)	934 (26.3)	801 (28.9)	527 (28.5)	205 (27.3)	401 (28.2)
Quartile 4 Most deprived	2768 (28.6)	1142 (32.2)	831 (28.9)	644 (34.8)	265 (35.3)	379 (26.7)

**Deprivation measured using the Index of Multiple Deprivation; HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 3: Multimorbidity transitions across A&E and hospital admission interface over 3-years

Study Groups[†]	A & E episodes				Hospital admissions			
	0	1	2	3	0	1	2	3
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*
HT+ DM-	26019 (68.6)	8903 (23.5)	2466 (6.5)	548 (1.4)	21957 (54.0)	10443 (27.5)	4223 (11.1)	1313 (3.5)
DM+ HT-	2733 (63.2)	1154 (26.4)	372 (8.4)	96 (2.1)	2343 (54.0)	1192 (27.5)	601 (13.8)	204 (4.7)
HT & DM	6168 (63.4)	2581 (26.5)	776 (8.0)	210 (2.2)	4800 (49.3)	2888 (29.7)	1456 (15.0)	591 (6.1)
DM+ CHD-	7048 (67.1)	2580 (24.6)	703 (6.7)	170 (1.6)	5766 (54.9)	2993 (28.2)	1403 (12.7)	490 (4.2)
CHD+ DM-	6223 (57.6)	3175 (29.4)	1133 (10.5)	276 (2.6)	4842 (44.8)	3482 (32.2)	1813 (16.8)	670 (6.2)
DM & CHD	1863 (52.1)	1145 (32.0)	436 (12.2)	130 (3.6)	1377 (38.5)	1123 (31.4)	721 (20.2)	353 (9.9)
DM+ CKD-	7440 (66.5)	2761 (24.7)	775 (6.9)	205 (1.8)	6083 (54.4)	3142 (28.1)	1438 (12.9)	518 (4.6)
CKD+ DM-	5137 (57.3)	2733 (30.5)	893 (10.0)	195 (2.2)	3923 (43.8)	3056 (34.1)	1502 (16.8)	477 (5.3)
DM & CKD	1471 (50.8)	964 (33.3)	364 (12.6)	95 (3.3)	1060 (36.6)	938 (32.4)	619 (21.4)	277 (9.6)
COPD+ CHD-	3013 (56.8)	1568 (29.6)	546 (10.3)	177 (3.3)	2443 (46.1)	1665 (31.4)	843 (15.9)	353 (6.7)
CHD+ COPD-	7267 (58.0)	3689 (29.5)	1261 (10.1)	309 (2.5)	5641 (45.0)	3973 (31.7)	2108 (16.8)	804 (6.4)
COPD & CHD	819 (44.2)	631 (34.0)	308 (16.6)	97 (5.2)	578 (31.2)	632 (34.1)	426 (23.0)	219 (11.8)

COPD+ CHF-	3519 (54.9)	1940 (30.3)	723 (11.3)	223 (3.5)	2810 (43.9)	2018 (31.5)	1102 (17.2)	475 (7.4)
CHF+ COPD-	1346 (46.7)	990 (34.3)	440 (15.3)	108 (3.7)	978 (33.9)	996 (34.5)	645 (22.4)	265 (9.2)
CHF & COPD	313 (41.5)	259 (34.4)	131 (17.4)	51 (6.8)	211 (28.0)	279 (37.0)	167 (22.1)	97 (12.9)
CHF+ CKD-	1173 (53.0)	665 (30.0)	295 (13.3)	80 (3.6)	884 (39.9)	737 (33.3)	414 (18.7)	178 (8.0)
CKD+ CHF-	6122 (58.7)	3113 (29.9)	981 (9.4)	211 (2.0)	4678 (44.9)	3456 (33.1)	1723 (16.5)	570 (5.5)
CKD & CHF	481 (33.4)	595 (41.3)	284 (19.7)	80 (5.6)	305 (21.4)	538 (37.8)	398 (27.9)	184 (12.9)

† *minus sign indicates absence of disease and positive sign indicates presence, HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 4: Multimorbidity transitions across A&E episodes and hospital admissions and associated costs over 3-years

Study Groups	3-year AE £ costs Mean (SD)	Adjusted Regression* Estimates £ (SE)	*p*-value	3-year IP £ costs Mean (SD)	Adjusted Regression* Estimates £ (SE)	*p*-value
HT+ DM-	55 (132)	0		1647 (4085)	0	
DM+ HT-	69 (162)	20 (2)	<.001	2061 (4490)	595 (68)	<.001
HT & DM	69 (152)	14 (2)	<.001	2289 (4585)	607 (48)	<.001
DM+ CHD-	57 (124)	0		1825 (3977)	0	
CHD+ DM-	84 (175)	22 (2)	<.001	2512 (5825)	431 (73)	<.001
DM & CHD	104 (219)	42 (3)	<.001	3372 (5789)	1270 (101)	<.001
DM+ CKD-	60 (143)	0		1850 (3996)	0	
CKD+ DM-	80 (144)	4 (2)	0.14	2559 (4380)	403 (73)	<.001
DM & CKD	105 (190)	30 (3)	<.001	3642 (6063)	1480 (97)	<.001
COPD+ CHD-	96 (214)	0		2642 (4814)	0	
CHD+ COPD-	81 (180)	-13 (4)	<.001	2537 (5812)	-152 (92)	.097
COPD & CHD	138 (219)	40 (5)	<.001	3992 (5775)	1158 (151)	<.001
COPD+ CHF-	100 (211)	0		2769 (4925)	0	
CHF+ COPD-	120 (192)	17 (5)	<.001	3877 (5732)	904 (125)	<.001
CHF & COPD	166 (242)	64 (8)	<.001	4901 (6199)	1954 (206)	<.001
CHF+ CKD-	108 (176)	0		3282 (4880)	0	
CKD+ CHF-	75 (139)	-31 (4)	<.001	2477 (4404)	-629 (114)	<.001
CKD & CHF	164 (238)	52 (5)	<.001	5344 (6907)	2116 (163)	<.001

HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease
**Adjusted for age, gender and deprivation as measured by the Index of Multiple deprivation*

Title: Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

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Abstract

Objective: To investigate multimorbidity transitions from general practice populations across healthcare interfaces and the associated healthcare costs.

Design: Clinical-linkage database study.

Setting: Population (N=60,660) aged 40 years and over registered with 53 general practices in Stoke-on-Trent.

Participants: Population with six specified multimorbidity pairs were identified based on hypertension, diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and chronic kidney disease (CKD).

Main outcomes measures: Chronic disease registers were linked to accident and emergency (A&E) and hospital admissions for a 3-year time-period (2007-2009), and associated costs measured by Healthcare Resource Groups. Associations between multimorbid groups and direct healthcare costs were compared to their respective single disease groups using linear regression methods, adjusting for age, gender and deprivation.

Results: In the study population, there were 9735 patients with hypertension and diabetes (16%), 3574 with diabetes and CHD (6%), 2894 with diabetes and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%).

Transition defined as at least one episode in each of the three year time-period, were as follows: patients with hypertension and DM had the fewest transitions in the 3-year time-period (37% A&E episode and 51% hospital admission), but CHF and CKD has the most transitions (67% A&E episode and 79% hospital admission).

The average 3-year total costs per multimorbid patient for A&E episodes ranged from £69 to £166 and for hospital admissions ranged from between £2289 to £5344. The adjusted costs were significantly higher for all six multimorbid groups compared to their respective single disease groups.

Conclusions: Specific common multimorbid pairs are associated with higher healthcare transitions and differential costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of integrated care.

Article summary

Article focus

- In the population there are large numbers of people who suffer with two or multiple chronic diseases at the same time.
- Most of the current evidence has focused on the impact of multimorbidity on health status and very few have investigated the transitions across healthcare and the associated costs.
- Whilst individual chronic diseases have been shown to be associated with high health care costs, whether specific multimorbid combinations have differential healthcare transitions and healthcare costs is unknown.

Key messages

- Specific multimorbid pairs are associated with different levels of healthcare transitions and costs relating to accident and emergency and to hospital admissions.
- Chronic disease pairs indicate the population level multimorbidity 'severity' as indicated by transitions and costs, with a range from diabetes and hypertension ('low severity'), diabetes and heart disease, diabetes and chronic kidney disease, COPD and heart disease, heart failure & COPD, to heart failure and chronic kidney disease ('high severity').
- Identification of multimorbidity type and linkage of information across healthcare interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

Strengths and limitations of this study

- The study was based on large scale data linking chronic disease registers from general practices to A&E episodes and hospital admissions
- The study highlights the innovative potential of linkage data between healthcare interfaces to inform healthcare delivery
- The study uses a specific, but a limited number of common chronic diseases to illustrate the approach to using linked data within a single large region of the UK

Background

Multimorbidity is an individual's experience of two or more illnesses at the same time. In ageing populations the numbers of people with such multimorbidity will increase substantially, and it is estimated that there are up to 20% of the British population (4 million people) who may experience such multimorbidity[1], with a projected further increase of 37% in the England & Wales population aged 50 years and over by the year 2031. This means that the current focus of health care delivery on specific disease-focus outcomes will have to be complemented by a Public Health priority focusing on multimorbidity in older populations.

Current evidence on multiple disease in the same person has shown that this is a common problem, which has high impact on an individual's health and on the use of health care resources.[2,3,4] However, people may also experience transitions i.e. health care changes from general practice to different healthcare interfaces such as Accident and Emergency or hospital care, especially as delivery of chronic disease is orientated around individual healthcare pathways. Once a person experiences a number of different diseases, the issue then becomes how the person interacts with different healthcare interfaces. Current research has shown that in specific settings, such as general practice[5] or hospitals, multimorbidity is common in the encounters that are present in the disease-care pathways.[6,7] However, there is little empirical data on how multimorbidity influences transitions across different healthcare interfaces and whether specific multimorbidity combinations are more likely to be associated with higher healthcare presentations, such as Accident and Emergency (A&E) episodes or hospital admissions. Routine coding of such patients encounters now occurs in clinical practice, A&E and hospitals, and technological developments allow the linkage of clinical information across these interfaces.[8] These developments allow for the potential for targeted prevention and new models of healthcare interventions for patients who experience multiple chronic diseases at the same time.

The other key area of focus is how cost-effective care pathways can be developed. By understanding how multimorbidity influences interface presentation and the associated healthcare costs, it can be explored as to whether healthcare cost can be 'benchmarked' for specific conditions and combinations of conditions.[9] Currently much of the chronic disease healthcare delivery pathways has aligned along single-disease lines, for example diabetes, chronic obstructive airways disease or heart failure. So the potential range of multimorbidity model of care could range from joint clinics (e.g. diabetes and

renal) to the holistic clinical assessment conducted by elderly care physicians.[10,11] However, one could argue the next simple step from single disease pathway care to a multimorbidity approach, is understanding pair combinations which link to at least two individual disease care pathways, and which we use in this study by selecting common chronic diseases in the older population. Using a large linkage dataset we investigated the clinical hypothesis as to whether specific chronic disease multimorbidity pairs are associated with differences in health care transitions and associated healthcare costs, and compared to populations with only one of the respective matched conditions.

Methods

Design

The design of the study was a cross-sectional clinical linkage study of the population aged 40 years and over on chronic disease registers to transition data on A&E episode or hospital admission in a 3-year time-period (1st January 2007 to 31st December 2009).

Setting

The setting is an urban population of around 240,000 which focuses around the city of Stoke-on-Trent, which is one of the most deprived in England & Wales and has some of the highest levels of chronic disease prevalence and over half of areas are in the most deprived 20% in England.[12]

Clinical linkage datasets

Chronic disease registers

The local Primary Care Trust oversees 53 general practices and all practices have been participating in a national and local quality improvement framework[13] for specific chronic diseases, and in recording clinical data through regular data audits and checks. For specified conditions, using the Read Code classification[14], General Practitioners (GPs) and their teams had recorded clinical data on disease registers for their population. These practices contributed to the construction of a clinical database, which for this study covers a 3-year time-period. From this database, all adults on chronic disease registers for the following six conditions were identified: hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and chronic kidney disease (CKD).

Multimorbidity definitions

Whilst multimorbidity could be characterised for the study as any number or multiple combinations, we selected 'pairs' as the basic measure of investigating multimorbidity. The 'pairs' provides the basis for clinically intuitive understanding of how two chronic disease pathways might combine together, but with six study chronic diseases chosen, the potential number of pairs could be 6x6=36. Therefore, six example pairs were chosen to represent the range of chronic diseases onsets from mid-life to old-age and included: (i) DM and HT; (ii) DM and CHD; (iii) DM and CKD; (iv) COPD and CHD; (v) COPD and CHF; and (vi) CHF and CKD. These multimorbid pairs were then compared to their respective 'index' conditions, for example, HT and DM multimorbidity was compared to the group with HT without DM (expressed as HT+ DM-) and DM without HT (DM+ HT-). Each multimorbid group and their respective 'index' conditions represent a within group (see **Table 1** for annotation of all study defined groups) and separate clinical hypothesis of the association between multimorbidity and healthcare outcomes. Whilst this approach means that there might be overlap between multimorbid pair groups, each study group had been selected by common conditions of interest, and not in relation to other multimorbidity that might be present or absent.

In addition to age and gender data available from the general practice records, and the Index of Multiple Deprivation (IMD) was used as a measure of socio-economic status. The IMD is a measure of multiple deprivation at the small area level.[15] Based on Census data the score combines a number of indicators, including economic, social and housing issues, into a single deprivation score for each small area in England.

Healthcare transitions data: A&E episodes and hospital admissions

Using the unique NHS Number allocated to an individual patient, a dataset was created linking their clinical data from general practice to any other information such as A&E attendance and hospital admissions (planned and unplanned) for the time period 1st January 2007 to 31st December 2009. The total number of attendances in the study time period for each A&E type including minor injury units and walk-in centres were included. Whilst there are a number of hospital providers within the region, the single major provider of emergency and acute hospital services for the city is the University Hospital of North Staffordshire (UHNS) NHS Trust. Hospital admissions were based on Hospital Episode Statistics (HES), which contain records for all NHS patients admitted to any English hospitals in each financial year. These A&E and hospital data are means by

which Primary Care (PCT) Commissioners arrange payment from the purchaser to the acute hospital Trust provider.[16] Linking these clinical databases make it possible to track healthcare patterns of individual patients. We used these data therefore to establish the natural history of patients with multimorbidity and transitions across the A&E and hospital interfaces.

Healthcare transitions cost

For each transition activity, the allocated Healthcare Resource Group (HRG) was used as a measure of cost for an A&E episode or a hospital admission in the 3-year time-period. A HRG is a group of clinically similar treatments and care that require similar levels of healthcare resource. It allows commissioners to understand their activity in terms of the types of patients they care for and the treatments they undertake.[17,18] HRGs are currently used as a means of determining cost for individual patients in each financial year, depending on their healthcare use. From the individual-level HRG cost data for A&E episode or hospital admission, data was aggregated to the population-level costs for the specified multimorbidity groups for the whole of the 3-year time-period. Individual-level data were anonymised by the Public Health Intelligence Team and subsequently linked for analyses using study identifier by the project team, and provision of the anonymous data was made under existing service agreements.

Analyses

The multimorbidity populations are described by age bands (40-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, 90 years and over), gender and deprivation. The IMD score for the study population was summarised into quartiles ranging from quartile 1 (least deprived) to quartile 4 (most deprived). The socio-demographic prevalence for the study multimorbidity pairs and respective index conditions, including the population without index condition was also estimated and information is given in **Supplementary tables 1 to 3**.

Interface transitions for the six multimorbid groups and their respective index conditions were defined as follows. A&E transitions were first summarised as at least one episode in any one of the 3 years, and so does not include multiple episodes within the same year. A similar approach was used for summarising the hospital admissions. Chi square tests were used to assess trends in the association between study defined groups and recurrent A&E episodes and hospital admissions (defined as at least one in each of the

3 years). These data are then presented as counts measured from 0 (no episodes or admissions), 1 (one episode in any one of the 3 years), 2 (two episodes in any two of the 3 years), and 3 (at least one episode in all 3 years). ANOVA and ANCOVA with actual age, gender and IMD as covariates were used to estimate the significance of mean differences of number of A&E episodes, hospital admissions and costs, within each of the multimorbid groups, comparing the pairs of diseases to their respective index diseases.

Total costs for the study time period were estimated for each individual patient who had any A&E episode or hospital admissions, and here the total costs relate to all A&E episodes and hospital admissions over the 3 year time-period. Using linear regression methods, the difference in total cost per patient over the 3 years for each multimorbid group was compared to the respective index conditions was assessed, adjusting for age, gender and deprivation. Within each of the six multimorbid groups, the regression coefficient was tested for significance differences from their respective reference category with cost allocation as zero (0).

Results

From a study population of 60,660 patients aged 40 years and over on specific chronic disease registers in a 3-year time-period, there were 9735 patients with HT and DM (16%), 3574 with DM and CHD (6%), 2894 with DM and CKD (5%), 1855 with COPD and CHD (3%), 754 with CHF and COPD (1%), and 1425 with CHF and CKD (2%). The socio-demographic prevalence figures for the multimorbidity pair groups and comparator groups are given in **Supplementary Tables 1 to 3**.

Socio-demographic characteristics of multimorbid pairs

Multimorbid pairs, which included DM and HT or CHD, showed age-related differences (**Table 2**). Within the DM and CKD multimorbid group, there was a higher proportion of older patients aged 70 years and over (51%), than within the DM and CHD group or the HT and DM multimorbid group. There were more women (64%) than men within the DM and CKD group, than the other two DM multimorbid groups, but the deprivation distributions were similar. Within the COPD and CHF multimorbid groups, there was a higher proportion of older patients aged 70 years and over (75%), compared to COPD and CHD, but within the COPD and CHD group there were more men (62%) than

women. The CHF and CKD multimorbid group had the highest proportion who were aged 80 years and over (50%), and this group had more women than men.

Multimorbidity transitions across accident & emergency interface

Patients with HT and DM had the highest proportion without an A&E episode in the 3-year time-period (63%), but the patients with CKD and CHF had the lowest proportion without an A&E episode in the 3-year time-period (33%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 52%; DM & CKD 51%; COPD & CHD 44%; and CHF & COPD 42%.

The proportion of patients with recurrent A&E episodes (defined as at least one episode in each of the 3 years) for multimorbid groups was as follows: HT and DM 2%, DM & CHD 4%, DM & CKD 3%, COPD & CHD 5%, CHF & COPD 7% and CKD & CHF 6%. These associations and increase across the groups was even more evident for patients who had had an A&E episode in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and recurrent A&E episodes (p<0.001).

Multimorbidity transitions across hospital admission interface

Patients with HT and DM had the highest proportion without a hospital admission in the 3-year time-period (49%), but the patients with CKD and CHF had the lowest proportion without a hospital admission in the 3-year time-period (21%) (**Table 3**). The same figures for other multimorbid groups were as follows: DM & CHD 39%; DM & CKD 37%; COPD & CHD 31%; and CHF & COPD 28%.

The proportion of patients with recurrent hospital admissions (defined as at least one in each of the 3 years) for multimorbid groups was as follows: HT and DM 6%; DM & CHD 10%; DM & CKD 10%; COPD & CHD 12%; CHF & COPD 13%; and CKD & CHF 13%. These associations and increase across the groups was even more evident for patients who had had a hospital admission in any two of the three years (**Table 3**).

For all six groups, when multimorbid pairs were compared to their respective index conditions, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission (p<0.001).

Health care costs at the accident & emergency transition

Patients with HT and DM had the lowest mean A&E costs in the 3-year time-period (total £69), but the highest figure was for patients with CHF and COPD or CKD (around £166) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £104; DM & CKD £105; COPD & CHD £138; and CHF & COPD £164.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher A&E costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The A&E costs were £13 lower for the index CHD group compared to index COPD group, and £31 lower for index CKD group than the CHF group (**Table 3**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher A&E costs (p<0.001).

Healthcare costs at the hospital admission transition

Patients with HT and DM had the lowest mean hospital admissions costs in the 3-year time-period (total £2289), but patients with CHF and CKD had the highest costs (£5344) (**Table 4**). The same figures for other multimorbid groups were as follows: DM & CHD £3372; DM & CKD £3642; COPD & CHD £3992; and CHF & COPD £4901.

Adjusting for age, gender and deprivation, still showed that each of the six multimorbid groups had significantly higher hospital admission costs than their respective index diseases. When associations between multimorbid groups and costs were adjusted, there were two notable groups. The hospital admission costs were £152 lower for the index CHD group compared to index COPD group, and £629 lower for index CKD group than the CHF group (**Table 4**). For all six groups, when multimorbid pairs were compared to their respective index condition, there was an increasing and highly significant trend in the association between multimorbidity and higher hospital admission costs (p<0.001).

The six multimorbid groups were selected on the basis of age-related onsets. However, comparing the findings for the six multimorbid pairs, after age adjustment, also showed that these groups can be placed into an order of an increasing association between the 'severity' of multimorbid pair and the likelihood of A&E episodes and associated costs, or hospital admissions and associated costs over the 3-year time-period. The 'severity' of health care impact can be ordered as follows: DM and HT ('low severity'), DM and CHD,

DM and CKD, COPD and CHD, CHF & COPD, and CHF and CKD ('high severity') (**Tables 3 and 4**).

Discussion

Our large scale study in a chronic disease population showed that patients with specific multimorbidity pairs had distinct variations in healthcare transitions and in the associated healthcare costs. Whilst age is a specific indicator for the type of multiple chronic disease, adjustment for socio-demographic factors, still showed that specific multimorbidity pairs were associated with higher number of healthcare transitions compared to their respective index groups. Furthermore, these multimorbidity associations suggest that they can be ordered into a 'severity of healthcare impact', after adjusting for age. In this spectrum, multimorbidity such as hypertension and diabetes represents one end of the healthcare cost spectrum and chronic heart failure and chronic kidney disease representing the higher and most costly end of healthcare impact.

The implications of this multimorbidity study covering a 3-year time-period relates to the number of transitions and costs of transitions. The study shows that patients with specific multimorbidity has higher number of annual A&E episodes or hospital admissions and costs, which means that this provides a potential mechanism for targeting patients for intervention across the healthcare interfaces. Since this information could potentially be linked across the interface, it also provides the basis for intervention once initial transitions have occurred to prevent future unnecessary transitions from general practice to A&E or hospital admission.

The study was based on large scale data available from 53 general practices in one of the most deprived regions in England and over a long term time period of 3 years. The current national quality improvements approaches have been based on establishing chronic disease registers in clinical practice and aim at improving care for the individual patient.[12,19] However such registers also provide the basis for defining population-level impacts and for providing the integration between public health prevention (general practice or local area) and individual-level care. The definition of multimorbidity, focusing on 'pairs' also means that it allows easier interpretation of the current individual pathways of care and begins to provide insight into how these might be integrated. For example, hypertension, diabetes and coronary heart disease are often jointly managed in general practice, but in healthcare transitions, specialist care could be delivered by

nephrology (hypertension), diabetes or cardiology. However in severe chronic disease states, such as COPD, CHF and CKD, which are often jointly managed between general practice and hospital-based care, such 'multimorbidity pair' approach allows for the integration of care for high cost patients who may be cared for by several healthcare teams in different individual care pathways.

Whilst this was a large scale study, the cross-sectional findings relate to one region of England. The patterns of transitions may differ in other regions, especially as services moved to different integrated models, but the relative associations for multimorbid groups compared to the index groups provide the best available estimates on the impact on transitions and costs. These cost estimations and relative are conservative as the reference comparison groups had one of the two multimorbid conditions, whereas a non-index reference group without either pair condition would have magnified the relative cost differences. Whilst new integrated models of care are developing[20], such care will still need to differentiate between the acute health needs of the patient with a chronic disease addressed by specialist intervention, and the chronic health needs and monitoring that will be addressed by general practice and community teams. The study definitions also focused on pairs of conditions but all groups were not exclusive, and there was some overlap. For example diabetes was paired with hypertension, coronary heart disease and chronic kidney disease, which indicates an overlap, but these results showed that different pairs with the same index condition (e.g. diabetes) have distinct associations with healthcare transitions and costs.

The chronic disease registers from general practice were part of local and national initiatives, and such data are now used widely in performance and payment reporting, and healthcare studies.[19] The healthcare transition data also are part of national performance and payment reporting, and have also been used in healthcare studies. The recording of these transition episodes (A&E or hospital admission) will be accurate as the healthcare costs are based on the HRG allocated to each individual patient, and which is part of the cost transaction process between healthcare commissioner (PCT) and the provider (hospital). Furthermore the transitions data and cost data are part of national validation processes.[16,21] In this study, the primary objective was to test the clinical hypothesis that different multimorbidity pairs showed variations in overall healthcare transitions, and therefore does not include the attempt to characterise the precise nature of each transition episode. The estimated costs for these patient

populations are also an under-estimate since they do not include ongoing healthcare costs in general practice and community care.

Previously there have been few studies on multimorbidity and costs in specific settings[22,23], but there is a lack of healthcare transitions data, and the hypothesis that a study of specific 'disease pairs' may provide insight into healthcare presentation and costs has not been previously tested. Much of the current multimorbidity research has focused on the 'burden' as exemplified by the number of conditions that patient's experience, but the key limitation with the 'counting' approach is the lack of differentiation of how it links into the current individual disease-designed pathways. Arguably, it is better conceptualise this issue into 'which pairs' and link it practically to the individual disease pathways which have been devised in terms of chronic disease model of care.[24] Notably the notion of chronic disease and depression has been well constructed in the psychiatric field.[25] This 'disease pair' approach provides a simple and clinically intuitively approach that can be readily used in actual clinical practice, and a means by which local policy decisions can incorporate estimated costs for healthcare transitions.

This cross-sectional study provides the basis for the innovative linking of data, and understanding the healthcare 'journey' for the patient with different chronic diseases. Further studies would address issues such as multiple healthcare transitions, combining different interfaces (for example, identifying patients who attend A&E regularly and are admitted regularly) and the underlying and precise clinical reasons for the healthcare costs. For example, healthcare transitions may cover community care, and wider transitions could include social care. The associations shown in this study also need to be complemented by the temporal investigation between chronic disease pairs and subsequent impact on the time between health care transitions.

In conclusion, our study showed that specific multimorbid pairs compared to their index morbidity, indicated the level of transitions across healthcare interfaces and the associated total healthcare costs. Identification of multimorbidity type and linkage of information across interfaces provides opportunities for targeted intervention and delivery of cost-effective integrated care.

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Table 1: Study groups

Annotation	Study groups
HT+ DM-	Hypertension *without* diabetes mellitus
DM+ HT-	Diabetes mellitus *without* hypertension
HT & DM	Multimorbidity of hypertension *and* diabetes mellitus
DM+ CHD-	Diabetes mellitus *without* coronary heart disease
CHD+ DM-	Coronary heart disease *without* diabetes mellitus
DM & CHD	Multimorbidity of diabetes mellitus *and* coronary heart disease
DM+ CKD-	Diabetes mellitus *without* chronic kidney disease
CKD+ DM-	Chronic kidney disease *without* diabetes mellitus
DM & CKD	Multimorbidity of diabetes mellitus *and* chronic kidney disease
COPD+ CHD-	Chronic obstructive pulmonary disease *without* coronary heart disease
CHD+ COPD-	Coronary heart disease *without* chronic obstructive pulmonary disease
COPD & CHD	Multimorbidity of chronic obstructive pulmonary disease *and* coronary heart disease
COPD+ CHF-	Chronic obstructive pulmonary disease *without* chronic heart failure
CHF+ COPD-	Chronic heart failure *without* chronic obstructive pulmonary disease
CHF & COPD	Multimorbidity of chronic heart failure *and* chronic obstructive pulmonary disease
CHF+ CKD-	Chronic heart failure *without* chronic kidney disease
CKD+ CHF-	Chronic kidney disease *without* chronic heart failure
CKD & CHF	Multimorbidity of chronic kidney disease *and* chronic heart failure

Table 2: Socio-demographic characteristics of the multimorbid study pairs

Groups	HT & DM *No. (%)* (n=9735)	DM & CHD *No. (%)* (n=3574)	DM & CKD *No. (%)* (n=2894)	CHD & COPD *No. (%)* (n=1855)	CHF & COPD *No. (%)* (n=754)	CHF & CKD *No. (%)* (n=1425)
40-49 years	866 (8.9)	152 (4.2)	48 (1.7)	22 (1.2)	4 (0.5)	6 (0.4)
50-59 years	2043 (21.0)	533 (14.9)	227 (7.8)	179 (9.6)	42 (5.5)	49 (3.4)
60-69 years	2866 (29.4)	1067 (29.8)	645 (22.3)	499 (26.8)	140 (18.6)	177 (12.4)
70-79 years	2686 (27.6)	1219 (34.1)	1200 (41.3)	710 (38.3)	298 (39.3)	488 (34.2)
80-89 years	1152 (11.9)	552 (15.5)	691 (24.0)	409 (22.1)	236 (31.6)	594 (41.9)
90 years and over	122 (1.3)	51 (1.5)	83 (2.9)	36 (2.0)	34 (4.5)	111 (7.7)
Men	5016 (51.5)	2162 (60.4)	1055 (36.4)	1152 (62.1)	427 (56.4)	549 (38.5)
Women	4719 (48.5)	1412 (39.6)	1839 (63.6)	703 (37.9)	327 (43.6)	876 (61.5)
Quartile 1* Least deprived	2044 (21.1)	691 (19.5)	596 (20.7)	249 (13.5)	109 (14.5)	300 (21.1)
Quartile 2	2335 (24.1)	785 (22.1)	652 (22.6)	428 (23.2)	171 (22.8)	340 (23.9)
Quartile 3	2541 (26.2)	934 (26.3)	801 (28.9)	527 (28.5)	205 (27.3)	401 (28.2)
Quartile 4 Most deprived	2768 (28.6)	1142 (32.2)	831 (28.9)	644 (34.8)	265 (35.3)	379 (26.7)

**Deprivation measured using the Index of Multiple Deprivation; HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 3: Multimorbidity transitions across A&E and hospital admission interface over 3-years

Study Groups†	A & E episodes				Hospital admissions			
	0	1	2	3	0	1	2	3
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*
HT+ DM-	26019 (68.6)	8903 (23.5)	2466 (6.5)	548 (1.4)	21957 (54.0)	10443 (27.5)	4223 (11.1)	1313 (3.5)
DM+ HT-	2733 (63.2)	1154 (26.4)	372 (8.4)	96 (2.1)	2343 (54.0)	1192 (27.5)	601 (13.8)	204 (4.7)
HT & DM	6168 (63.4)	2581 (26.5)	776 (8.0)	210 (2.2)	4800 (49.3)	2888 (29.7)	1456 (15.0)	591 (6.1)
DM+ CHD-	7048 (67.1)	2580 (24.6)	703 (6.7)	170 (1.6)	5766 (54.9)	2993 (28.2)	1403 (12.7)	490 (4.2)
CHD+ DM-	6223 (57.6)	3175 (29.4)	1133 (10.5)	276 (2.6)	4842 (44.8)	3482 (32.2)	1813 (16.8)	670 (6.2)
DM & CHD	1863 (52.1)	1145 (32.0)	436 (12.2)	130 (3.6)	1377 (38.5)	1123 (31.4)	721 (20.2)	353 (9.9)
DM+ CKD-	7440 (66.5)	2761 (24.7)	775 (6.9)	205 (1.8)	6083 (54.4)	3142 (28.1)	1438 (12.9)	518 (4.6)
CKD+ DM-	5137 (57.3)	2733 (30.5)	893 (10.0)	195 (2.2)	3923 (43.8)	3056 (34.1)	1502 (16.8)	477 (5.3)
DM & CKD	1471 (50.8)	964 (33.3)	364 (12.6)	95 (3.3)	1060 (36.6)	938 (32.4)	619 (21.4)	277 (9.6)
COPD+ CHD-	3013 (56.8)	1568 (29.6)	546 (10.3)	177 (3.3)	2443 (46.1)	1665 (31.4)	843 (15.9)	353 (6.7)
CHD+ COPD-	7267 (58.0)	3689 (29.5)	1261 (10.1)	309 (2.5)	5641 (45.0)	3973 (31.7)	2108 (16.8)	804 (6.4)
COPD & CHD	819 (44.2)	631 (34.0)	308 (16.6)	97 (5.2)	578 (31.2)	632 (34.1)	426 (23.0)	219 (11.8)

COPD+ CHF-	3519 (54.9)	1940 (30.3)	723 (11.3)	223 (3.5)	2810 (43.9)	2018 (31.5)	1102 (17.2)	475 (7.4)
CHF+ COPD-	1346 (46.7)	990 (34.3)	440 (15.3)	108 (3.7)	978 (33.9)	996 (34.5)	645 (22.4)	265 (9.2)
CHF & COPD	313 (41.5)	259 (34.4)	131 (17.4)	51 (6.8)	211 (28.0)	279 (37.0)	167 (22.1)	97 (12.9)
CHF+ CKD-	1173 (53.0)	665 (30.0)	295 (13.3)	80 (3.6)	884 (39.9)	737 (33.3)	414 (18.7)	178 (8.0)
CKD+ CHF-	6122 (58.7)	3113 (29.9)	981 (9.4)	211 (2.0)	4678 (44.9)	3456 (33.1)	1723 (16.5)	570 (5.5)
CKD & CHF	481 (33.4)	595 (41.3)	284 (19.7)	80 (5.6)	305 (21.4)	538 (37.8)	398 (27.9)	184 (12.9)

† *minus sign indicates absence of disease and positive sign indicates presence, HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease*

Table 4: Multimorbidity transitions across A&E episodes and hospital admissions and associated costs over 3-years

Study Groups	3-year AE £ costs Mean (SD)	Adjusted Regression* Estimates £ (SE)	*p*-value	3-year IP £ costs Mean (SD)	Adjusted Regression* Estimates £ (SE)	*p*-value
HT+ DM-	55 (132)	0		1647 (4085)	0	
DM+ HT-	69 (162)	20 (2)	<.001	2061 (4490)	595 (68)	<.001
HT & DM	69 (152)	14 (2)	<.001	2289 (4585)	607 (48)	<.001
DM+ CHD-	57 (124)	0		1825 (3977)	0	
CHD+ DM-	84 (175)	22 (2)	<.001	2512 (5825)	431 (73)	<.001
DM & CHD	104 (219)	42 (3)	<.001	3372 (5789)	1270 (101)	<.001
DM+ CKD-	60 (143)	0		1850 (3996)	0	
CKD+ DM-	80 (144)	4 (2)	0.14	2559 (4380)	403 (73)	<.001
DM & CKD	105 (190)	30 (3)	<.001	3642 (6063)	1480 (97)	<.001
COPD+ CHD-	96 (214)	0		2642 (4814)	0	
CHD+ COPD-	81 (180)	-13 (4)	<.001	2537 (5812)	-152 (92)	.097
COPD & CHD	138 (219)	40 (5)	<.001	3992 (5775)	1158 (151)	<.001
COPD+ CHF-	100 (211)	0		2769 (4925)	0	
CHF+ COPD-	120 (192)	17 (5)	<.001	3877 (5732)	904 (125)	<.001
CHF & COPD	166 (242)	64 (8)	<.001	4901 (6199)	1954 (206)	<.001
CHF+ CKD-	108 (176)	0		3282 (4880)	0	
CKD+ CHF-	75 (139)	-31 (4)	<.001	2477 (4404)	-629 (114)	<.001
CKD & CHF	164 (238)	52 (5)	<.001	5344 (6907)	2116 (163)	<.001

HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease
**Adjusted for age, gender and deprivation as measured by the Index of Multiple deprivation*

STROBE Statement— Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *Clinical linkage study*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Structured abstract and key summary with limitations included*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *Rationale clear and importance*
Objectives	3	State specific objectives, including any prespecified hypotheses *Hypothesis included in the objectives*
Methods		
Study design	4	Present key elements of study design early in the paper *Design included at start of methods section*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Location and dates of data included*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants *Methods of selection though registers and multimorbidity pairs included*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *Transitions of healthcare outcome data included, and age, gender and deprivation as important confounders*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group *(i) Chronic disease measurement was based on registers from general practice data* *(ii) Hospital data based on Healthcare resource groups* *(iii) Age and gender based on clinical records* *(iv)Index of Multiple Deprivation based on postal codes enumeration district*
Bias	9	Describe any efforts to address potential sources of bias *Selection issues addressed by focusing on a large dataset and on chronic diseases which are part of performance incentives*
Study size	10	Explain how the study size was arrived at *This was a descriptive study so sample size estimation was not require*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *Rationale for methods and analyses included*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *Analyses section included*
		(*b*) Describe any methods used to examine subgroups and interactions *Sub-groups described in the multimorbidity definitions section*
		(*c*) Explain how missing data were addressed

		The only missing data was for the IMD score, but this was for only 0.5% of the data
		(*d*) If applicable, describe analytical methods taking account of sampling strategy *Analyses section included*
		(*e*) Describe any sensitivity analyses *Not required*
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *Detailed tables given including Supplementary tables*
		(b) Give reasons for non-participation at each stage *Not applicable*
		(c) Consider use of a flow diagram *Not applicable*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders *Detailed tables given including Supplementary tables*
		(b) Indicate number of participants with missing data for each variable of interest *Not applicable*
Outcome data	15*	Report numbers of outcome events or summary measures *Detailed tables given including Supplementary tables*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *In Table 3, we have given average unadjusted estimates and adjusted cost differences*
		(*b*) Report category boundaries when continuous variables were categorized *In Table 3, we have given Standard Deviations*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period *Not applicable*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses *Not applicable*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Included in the discussion section*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Included in the discussion section*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *Included in the discussion section*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Included in the discussion section*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	Not applicable

Supplementary Table 1: Socio-demographic characteristics of specific multimorbid study pairs

Groups N=60,660	HT- DM- n=8649	HT+ DM- n=37836	HT- DM+ n=4340	HT & DM n=9735	DM- CHD- n=35778	DM+ CHD- n=10501	DM- CHD+ n=10807	DM & CHD n=3574
40-49 years	776 (11.0)	4444 (63.2)	946 (13.5)	866 (12.3)	4621 (65.7)	1660 (23.6)	599 (8.5)	152 (2.2)
50-59 years	1730 (13.3)	8140 (62.4)	1135 (8.7)	2043 (15.7)	8202 (62.9)	2645 (20.3)	1668 (12.8)	533 (4.1)
60-69 years	2271 (14.1)	9922 (61.7)	1027 (6.4)	2866 (17.8)	9361 (58.2)	2826 (17.6)	2832 (17.6)	1067 (6.6)
70-79 years	2155 (14.6)	9140 (61.9)	792 (5.4)	2686 (18.2)	7996 (54.1)	2259 (15.3)	3299 (22.3)	1219 (8.3)
80-89 years	1409 (16.7)	5496 (65.3)	364 (4.3)	1152 (13.7)	4822 (57.3)	964 (11.4)	2083 (24.7)	552 (6.6)
90 years and over	308 (23.7)	794 (61.1)	76 (5.8)	122 (9.4)	776 (59.7)	147 (11.3)	326 (25.1)	51 (3.9)
Men	4620 (16.0)	16738 (57.9)	2512 (8.7)	5016 (17.4)	15065 (52.2)	5366 (18.6)	6293 (21.8)	2162 (7.5)
Women	4029 (12.7)	21198 (66.7)	1828 (5.8)	4719 (14.9)	20713 (65.2)	5135 (16.2)	4514 (14.2)	1412 (4.4)
Quartile 1* Least deprived	2005 (13.3)	10038 (66.8)	942 (6.3)	2044 (13.6)	9496 (63.2)	2295 (15.3)	2547 (16.9)	691 (4.6)
Quartile 2	2067 (13.8)	9596 (64.1)	972 (6.5)	2335 (15.6)	9022 (60.3)	2522 (16.8)	2641 (17.6)	785 (5.2)
Quartile 3	2210 (14.8)	9048 (60.7)	1115 (7.5)	2541 (17.0)	8602 (57.7)	2722 (18.3)	2656 (17.8)	934 (6.3)
Quartile 4 Most deprived	2328 (15.0)	9082 (58.7)	1291 (8.3)	2768 (17.9)	8502 (55.0)	2917 (18.9)	2908 (18.8)	1142 (7.4)

**Deprivation measured using the Index of Multiple Deprivation; HT=hypertension, DM=diabetes mellitus, CHD=coronary heart disease; *IMD scores available on 60382 patient; figures in brackets are a percentage of each socio-demographic factor; study sample selected by one of six registers (hypertension, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease, chronic heart failure and chronic kidney disease)*

Supplementary Table 2: Socio-demographic characteristics of specific multimorbid study pairs

Groups N=60,660	DM- CKD- n=37627	DM+ CKD- n=11181	DM- CKD+ n=8958	DM & CKD n=2894	COPD- CHD- n=40975	COPD+ CHD- n=12526	COPD- CHD+ n=5304	CHD & COPD n=1855
40-49 years	5026 (71.5)	1764 (25.1)	194 (2.8)	48 (0.7)	5918 (84.2)	729 (10.4)	363 (5.2)	22 (0.3)
50-59 years	9263 (71.0)	2951 (22.6)	607 (4.7)	227 (1.7)	9822 (75.3)	2022 (15.5)	1025 (7.9)	179 (1.4)
60-69 years	10480 (65.1)	3248 (20.2)	1713 (10.6)	645 (4.0)	10594 (65.9)	3400 (21.1)	1593 (9.9)	499 (3.1)
70-79 years	8073 (54.6)	2278 (15.4)	3222 (21.8)	1200 (8.1)	8760 (59.3)	3808 (25.8)	1495 (10.1)	710 (4.8)
80-89 years	4132 (49.1)	825 (9.8)	2773 (32.9)	691 (8.2)	5032 (59.8)	2226 (26.4)	754 (9.0)	409 (4.9)
90 years and over	653 (50.2)	115 (8.8)	449 (34.5)	83 (6.4)	849 (65.3)	341 (26.2)	74 (5.7)	36 (2.8)
Men	18790 (65.0)	6473 (22.4)	2568 (8.9)	1055 (3.7)	17625 (61.0)	7303 (25.3)	2806 (9.7)	1152 (4.0)
Women	18837 (59.3)	4708 (14.8)	6390 (20.1)	1839 (5.8)	23350 (73.5)	5223 (16.4)	2498 (7.9)	703 (2.2)
Quartile 1* Least deprived	9756 (64.9)	2390 (15.9)	2287 (15.2)	596 (4.0)	10901 (72.5)	2989 (19.9)	890 (5.9)	249 (1.7)
Quartile 2	9416 (62.9)	2655 (17.7)	2247 (15.0)	652 (4.4)	10389 (69.4)	2998 (20.0)	1155 (7.7)	428 (2.9)
Quartile 3	9055 (60.7)	2855 (19.1)	2203 (14.8)	801 (5.4)	9855 (66.1)	3063 (20.5)	1469 (9.8)	527 (3.5)
Quartile 4 Most deprived	9218 (59.6)	3228 (20.9)	2192 (14.2)	831 (5.4)	9655 (62.4)	3406 (22.0)	1764 (11.4)	644 (4.2)

**Deprivation measured using the Index of Multiple Deprivation; DM=diabetes mellitus, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease; *IMD scores available on 60382 patient; figures in brackets are a percentage of each socio-demographic factor; study sample selected by one of six registers (hypertension, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease, chronic heart failure and chronic kidney disease)*

Supplementary Table 3: Socio-demographic characteristics of specific multimorbid study pairs

Groups N=60,660	COPD- CHF- n=50617	COPD+ CHF- n=6405	COPD- CHF+ n=2884	CHF & COPD n=754	CHF- CKD- n=46595	CHF+ CKD- n=10427	CHF- CKD+ n=2213	CHF & CKD n=1425
40-49 years	6586 (93.7)	381 (5.4)	61 (0.9)	4 (0.1)	6731 (95.7)	236 (3.4)	59 (0.8)	6 (0.1)
50-59 years	11661 (89.4)	1162 (8.9)	183 (1.4)	42 (0.3)	12038 (92.3)	785 (6.0)	176 (1.3)	49 (0.4)
60-69 years	13504 (83.9)	1952 (12.1)	490 (3.0)	140 (0.9)	13275 (82.5)	2181 (13.6)	453 (2.8)	177 (1.1)
70-79 years	11665 (79.0)	1907 (12.9)	903 (6.1)	298 (2.0)	9638 (65.2)	3934 (26.6)	713 (4.8)	488 (3.3)
80-89 years	6262 (74.4)	927 (11.0)	996 (11.8)	236 (2.8)	4319 (51.3)	2870 (34.1)	638 (7.6)	594 (7.1)
90 years and over	939 (72.2)	76 (5.8)	251 (19.3)	34 (2.6)	594 (45.7)	421 (32.4)	174 (13.4)	111 (8.5)
Men	23623 (81.8)	3531 (12.2)	1305 (4.5)	427 (1.5)	24080 (83.4)	3074 (10.6)	1183 (4.1)	549 (1.9)
Women	26994 (85.0)	2874 (9.0)	1579 (5.0)	327 (1.0)	22515 (70.9)	7353 (23.1)	1030 (3.2)	876 (2.8)
Quartile 1* Least deprived	13244 (88.1)	1030 (6.9)	646 (4.3)	109 (0.7)	11691 (77.8)	2583 (17.2)	455 (3.0)	300 (2.0)
Quartile 2	12700 (84.8)	1412 (9.4)	687 (4.6)	171 (1.1)	11553 (77.2)	2559 (17.1)	518 (3.5)	340 (2.3)
Quartile 3	12157 (81.5)	1791 (12.0)	761 (5.1)	205 (1.4)	11345 (76.1)	2603 (17.5)	565 (3.8)	401 (2.7)
Quartile 4 Most deprived	12283 (79.4)	2143 (13.9)	778 (5.0)	265 (1.7)	11782 (76.2)	2644 (17.1)	664 (4.3)	379 (2.5)

**Deprivation measured using the Index of Multiple Deprivation; CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, CKD=chronic kidney disease; *IMD scores available on 60382 patient; figures in brackets are a percentage of each socio-demographic factor; study sample selected by one of six registers (hypertension, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease, chronic heart failure and chronic kidney disease)*